

MESO-SUBSTITUTED PORPHYRINS**Field of the invention**

The present invention refers to meso-substituted porphyrins of formula (I) hereinafter reported, the processes related to their preparation and use as photosensitising agents for therapeutic, diagnostic and photosterilisation uses.

State of the art

It is known that tetrapyrrolic macrocycles, like porphyrins or other photosensitisers, are able to preferentially localise in neoplastic tissues and, once photo-activated by irradiation with visible light, they are capable of generating hyper-reactive derivatives of oxygen such as radicals and singlet-oxygen. Due to their high intrinsic reactivity, these species trigger irreversible oxidative cytotoxic processes against cells and tissues, thus being highly cytotoxic after the localisation of the photosensitiser onto targets and irradiation.

Thanks to their properties, porphyrins are used as photosensitizers for the treatment of tumours in the so-called "photodynamic therapy" (hereinafter referred to as PDT).

A typical PDT protocol is based on the administration of an appropriate dose of photosensitizer, followed by irradiation of the tissues wherein the tumour is localised by using light of appropriate wavelength, thus causing, by the so-called photodynamic effect, the preferential or selective elimination of the tumour mass.

Due to the selective localisation in tumour tissues these photosensitizers can therefore be used not only for therapeutic purposes, but also as diagnostic agents as their high fluorescence quantum yield allow the direct visualisation of the tumour lesion.

Besides in the photoinactivation of tumour cells, it has been shown that photosensitizers can also be used in the treatment and diagnosis of pre-tumour pathologies and for various hyperproliferative diseases like psoriasis, actinic keratosis, atheromas, endoarterial hyperplasia and prostate hyperplasia, as well as for microbial photoinactivation and therefore in the treatment of bacterial and micotic infections.

Although the early use of porphyrins in PDT has given encouraging results, the compounds prepared until now need further improvements because of their

markedly limited efficiency and poor selectivity toward the eukaryotic cells and/or micro-organisms, and because of the prolonged persistence in the skin, which often may cause phenomena of generalised photosensitivity (Jori G., *J. Photochem. Photobiol., B: Biol.*, Vol. 36, pp. 87-93, 1996).

- 5 Thus it is evident how important it is to develop novel porphyrin compounds suitable for the use as therapeutic agents in PDT and as diagnostic agents, but not showing the limitations illustrated above.

Porphyrin derivatives bearing cationic groups have been previously described (Merchat et al. *J. Photochem. Photobiol.* 32, 153-157, 1996; Merchat et al. *J.*
10 *Photochem. Photobiol.* 35, 149-157, 1996) and assessed for their photodynamic properties in the bacteria photoinactivation. These compounds bear trimethyl-anilinium groups or quaternary ammonium pyridinium groups in the meso-positions and therefore are endowed by a hydrophilic nature.

Other photosensitisers such as phthalocyanines having hydrophilic and/or
15 amphiphilic characteristics are known; for example, the International Applications No. WO 01/96343 and WO 02/090361, and in the US Patent No. 5,965,598, all in the name of the Applicant, disclose various evenly substituted hydrophilic phthalocyanines, as well as non centrosymmetrical phthalocyanines bearing cationic or protonable group on the macrocycle.

20 **Summary of the invention**

The Applicant has now found a novel series of photosensitizers having particularly advantageous properties compared to the known compounds.

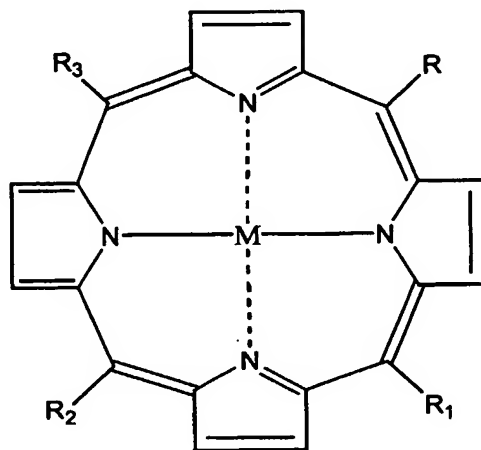
These novel compounds have shown optimum physical-chemical features for therapeutic applications, particularly in relation to their absorption in the region of
25 the visible spectrum, high molar extinction coefficients, high quantum yield in singlet oxygen production, that is expressed by the photoinactivation of eukaryotic and prokaryotic cells.

The photosensitizers described by this invention are able to produce singlet oxygen by using various light sources and wavelengths. In particular they can be
30 activated by visible red light radiation when the treatment of deep seated tumours on infections is required as well as by blue visible radiation or white light radiations when is preferable to treat by means of the photodynamic process more superficial

lesions such as in the treatment of psoriasis, actinic keratoses, basal cell carcinomas and other cancerous and pre-cancerous lesions of the skin and mucosas. Of particular interest is the possibility to modulate the activity of these products by acting on the radiation wavelength used for the activation. In fact it is well known that porphyrins are able to absorb light in the red region and in the blue region of the visible spectrum to a different extent. The combination of the light source devised to these purposes and the differential absorption by the porphyrins, allows a unique possibility in order to precisely define the activity of these compounds while used as photosensitizers in the photodynamic treatment of the above mentioned pathologies.

The present compounds are therefore suitable for the photodynamic treatment of pathologies characterised by cellular hyperproliferation and for the photodynamic treatment of infections caused by pathogenic micro-organisms, however can be also used as in vivo diagnostic agents due to the fluorescence released after excitation at various wavelength in the visible region of the light spectrum. Finally these derivatives can be used as sterilising agents in the in vivo treatment such as the treatment of wounds as well as in vitro treatments such as the blood or blood derivatives sterilisation.

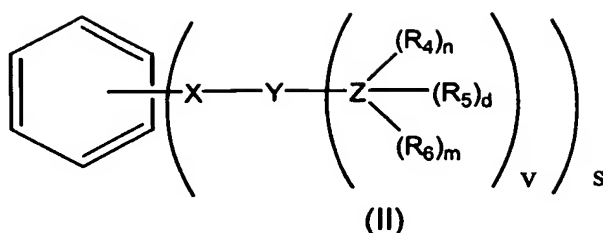
Subject of the present invention are therefore the porphyrins of general formula (I)



(I)

wherein

R is the following group of formula (II)



wherein

X is selected from the group consisting of O, S, CH₂, COO, CH₂CO, O(CH₂)₂O, O(CH₂)₃O and N;

5 Z is selected from between N and CH₂N;

Y is selected from aliphatic groups, linear or branched, saturated or unsaturated, having from 1 to 10 carbon atoms, and phenyl, possibly substituted, or Y forms with Z a saturated or unsaturated heterocycle, possibly substituted, comprising up to two heteroatoms selected from the group consisting of N, O and S;

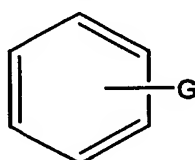
10 R₄ and R₅, equal or different from each other, are selected from H and alkyl groups having from 1 to 3 carbon atoms, or they form with the Z group a saturated or unsaturated heterocycle, possibly substituted, comprising up to two heteroatoms selected from the group consisting of N, O and S;

R₆ is selected from H and aliphatic groups, linear or branched, saturated or
15 unsaturated, having from 1 to 5 carbon atoms, possibly substituted with alkylamine or alkylammonium groups having alkyl chains comprising from 1 to 5 carbon atoms, or forming a saturated heterocycle comprising up to two heteroatoms selected from between O and N;

d, m, and n, equal or different from each other, are selected from 0 and 1;

20 v and s, equal or different from each other, are integers comprised between 1 and 3;

R₁ is selected from H and a group of formula (III)



(III)

wherein

25 G is selected from H and P- (CH₂)₁- (W)_f- J, wherein

P is selected from the group consisting of O, CH₂, CO₂, NHCONH and CONH;

l is an integer comprised between 0 and 5;

W is selected from the group consisting of O, CO₂, CONH and NHCONH;

f is selected from between 0 and 1;

5 J is H or an alkyl group (CH₂)_q-CH₃, wherein q is an integer comprised between 0 and 20;

R₂ and R₃, equal or different from each other, are selected from between R and R₁, wherein R and R₁ are defined as above,

M is chosen from 2H and a metal selected from the group consisting of Zn, Mg, Pt, Pd, Si(OR₇)₂, Ge(OR₇)₂ and AlOR₇, wherein R₇ is chosen from between H and C1-

10 C15 alkyl,

and pharmaceutically acceptable salts thereof.

Further subject of the present invention are the processes for the preparation of the above said compounds of formula (I), the novel intermediates in these processes and the conjugates in which the compounds of formula (I) are site

15 specifically conjugated with bio-organic carriers, such as aminoacids, polypeptides, proteins and polysaccharides.

The present compounds of formula (I), as well as the corresponding conjugates, are useful for the treatment of microbial infections (bacterial, fungal and viral), in the photodynamic treatment of tumour, pre-cancerous pathologies, and other

20 hyperproliferative diseases.

The present compounds (I) and the corresponding conjugates are useful as well, as diagnostic agents for the identification of pathologically affected areas and for photodynamic sterilization of blood and blood derivatives.

Features and advantages of the present compounds of formula (I) will be

25 illustrated in details in the following description.

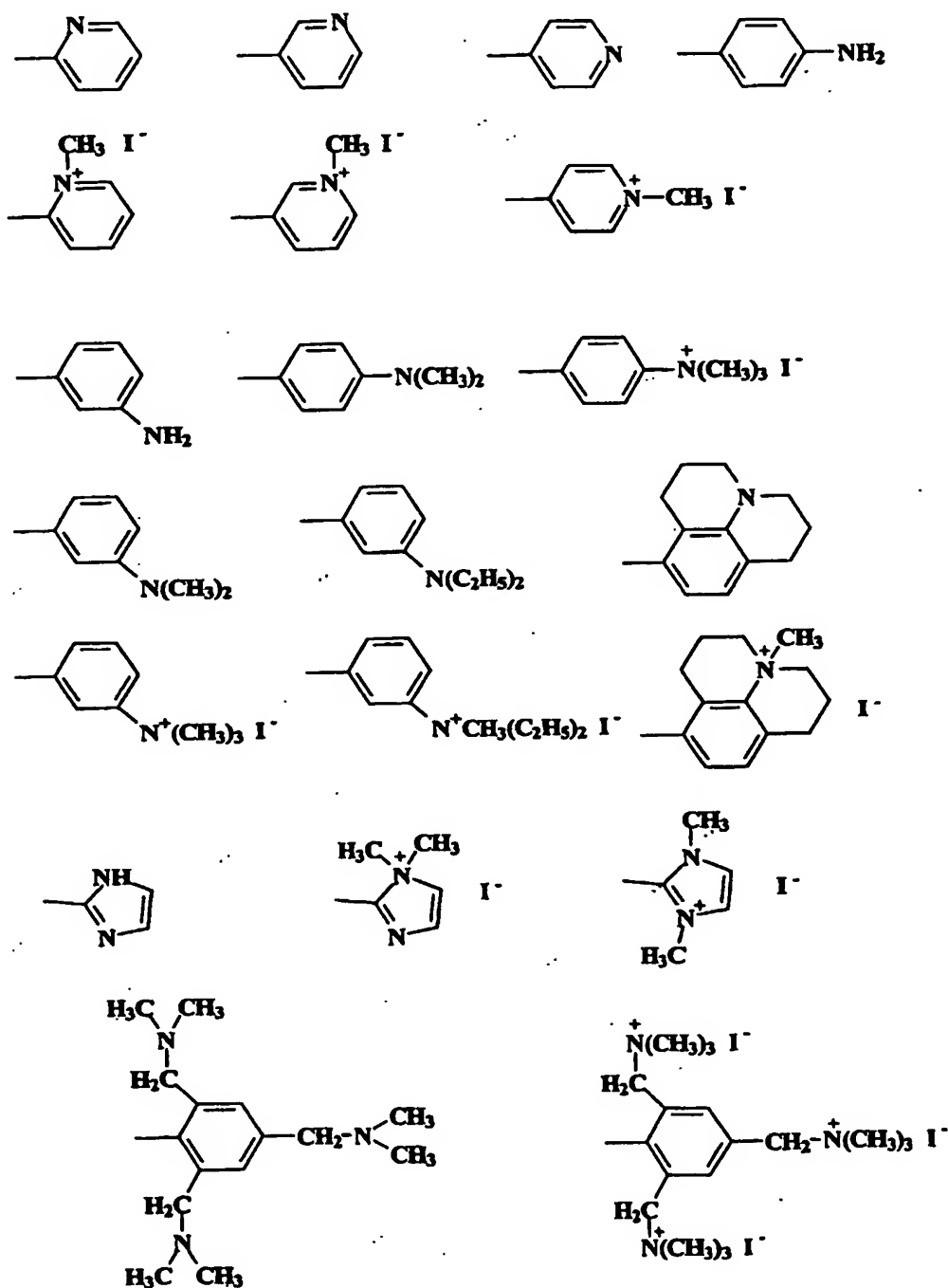
Detailed description of the invention

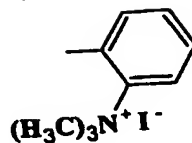
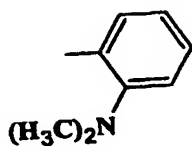
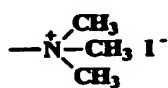
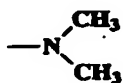
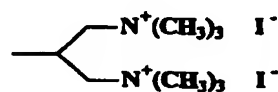
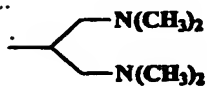
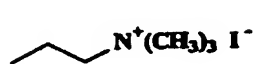
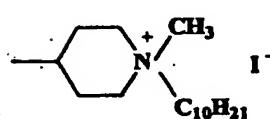
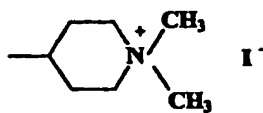
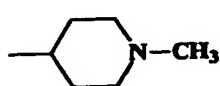
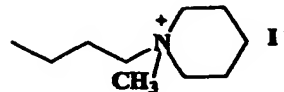
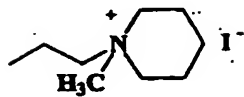
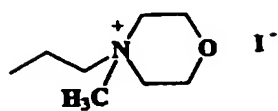
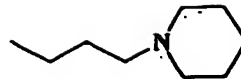
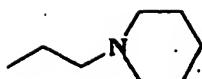
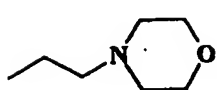
By "saturated or unsaturated heterocycle possibly substituted" according to the invention, an heterocycle is preferably meant, which is selected from the group consisting of morpholine, piperidine, pyridine, pyrimidine, piperazine, pyrrolidine, pyrroline, imidazole, aniline and julolidine (2,3,6,7-tetrahydro-1H,5H pirido[3,2,1-*l*] quinoline).

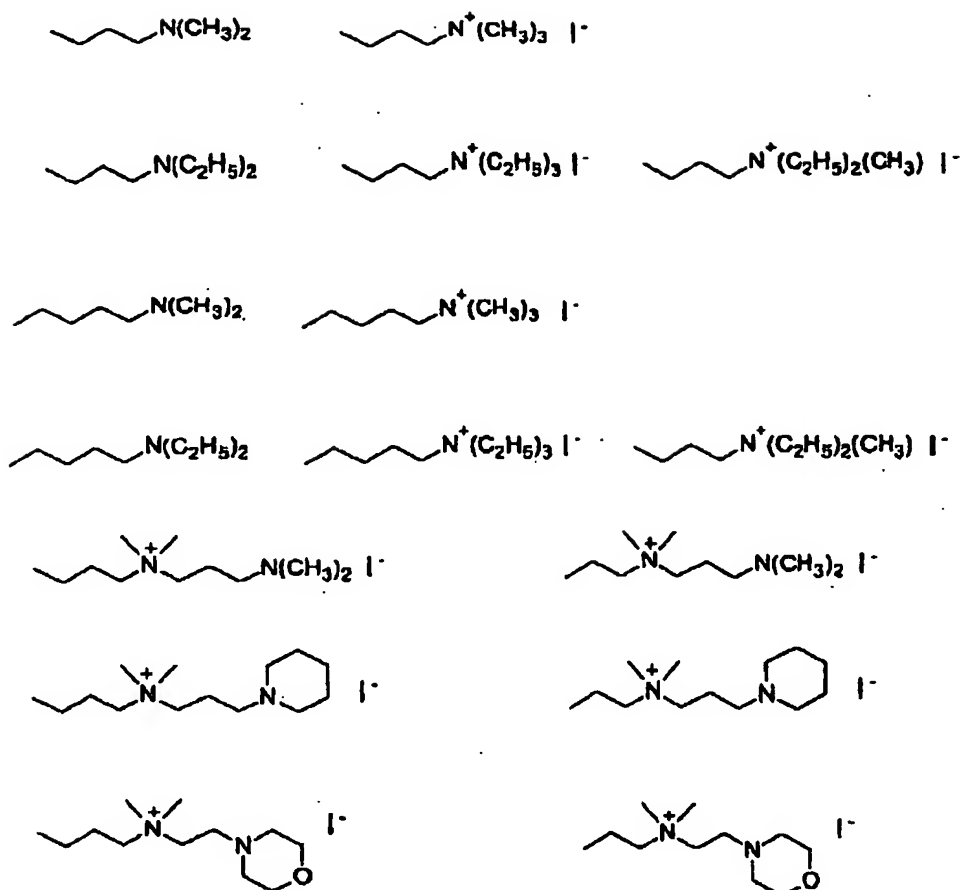
30

According to a particular embodiment of the invention, the present porphyrins of formula (I) have two or three groups with amino or ammonium substituents in two or three of the four meso-positions, and H or groups with non polar substituents on the other meso-positions.

- 5 Preferred compounds according to the invention are those wherein the group R comprises substituents bearing tertiary or quaternary nitrogen; more preferred are the present compounds of formula (I) wherein the group is selected from the group consisting of:







Pharmaceutically acceptable salts of porphyrins of general formula (I) according to the invention, bearing basic substituents, include conventional acid addition salts, obtained by the addition of HCl, H₃PO₄, H₂SO₄, HBr or by ion-exchange.

- 5 Additionally, salts obtained by reaction of a carboxylic function or acid groups with the porphyrin ring are within the scope of the present invention.

The present compounds of formula (I) show valuable photodynamic characteristics making them useful in photodynamic therapy (PDT) against bacterial, fungal, and viral infections, for various hyperproliferative diseases, as well as for
 10 photosterilization of blood and blood derivatives, such as platelets and erythrocytes. In this particular case the present compounds can be added to blood or blood derivatives as such or bound to suitable matrix, according to the known techniques, and thereafter irradiated. Moreover they can be used as diagnostic

agents for the identification of pathologically affected areas.

The present products possess a high molar absorption coefficient, which represents an important requirement for an effective therapeutic response.

They may be activated by tissue penetrating radiation having a wavelength around 650 nm, and hence they are suitable for the use in PDT against diseases, both dermatological and internal, but they also can be activated by using less tissue penetrating light for the photodynamic treatment of very superficial lesion, especially when a little damage of the skin should be accomplished or, for instance, when a fluorescence emission from the tissue is preferred such as in the photodiagnostic procedures of the above mentioned pathologies.

The products formed by photobleaching of the present compounds are non toxic. This finding reinforces their usefulness as therapeutic since, after having exploited their action, the compounds are inactivated by the light and then are no more potentially toxic *in vivo*.

The present compounds are active in the singlet oxygen production or allow the production of reactive species of oxygen under conditions of poor oxygenation. Such requirement is particularly important because it allows to treat specifically anaerobic micro-organisms or tumour cells, well-known characterised by an environment poor of oxygen.

In particular, the present compounds possess very high efficiency for micro-organisms such as yeasts, fungi and mycoplasma, Gram-positive and Gram-negative bacteria, and show a great ability in specifically localising on micro-organisms compared to the mammalian host cells.

The present invention comprises also the above described formula (I) compounds site-specifically conjugated with a bio-organic carrier able to direct to a definite target.

According to the invention the carrier is usually chosen among molecules having well-known specific binding capacities, for example aminoacids (preferably basic aminoacids), polypeptides (preferably consisting of basic aminoacids), proteins and polysaccharides normally used for targeting purposes.

The binding porphyrin/carrier may occur for example between the corresponding amino or carboxyl groups, or may occur involving other specific functional groups on the porphyrin moiety or on the carrier molecule.

Functional groups such as thiol, maleimide derivatives, α -bromo esters and amides, diazonium salts and azido derivatives can be introduced according to known procedures in order to pre-functionalise both the porphyrin or the carrier depending upon the selected carrier itself and its stability.

The compounds of the present invention can be prepared according to processes known in organic chemistry starting from suitable reagents. For example, when compounds of formula (I) in which $R = R_2 = R_3$ are desired, they can be prepared according to a process selected from the group consisting of:

- process comprising pre-functionalization of suitable reagents with amino groups, followed by statistical synthesis of the porphyrin ring, possible modification of the amino groups in ammonium groups, and possible complexation with the metal cation if the metal complex is required;
- process comprising statistical synthesis with formation of the porphyrin ring followed by functionalization of the porphyrin with the present amino or ammonium groups, and possible complexation with the metal cation; and
- process comprising synthesis of the porphyrin ring through suitable dipyrromethane derivatives followed by functionalisation of the porphyrin with the present amino or ammonium groups, and possible complexation with the metal cation.

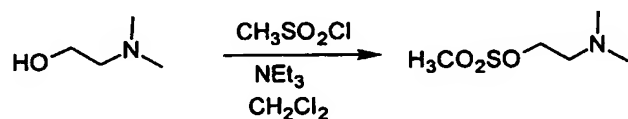
When compounds of formula (I) are desired in which $R = R_2$ and $R_1 = R_3$, they can be prepared for example according to a process comprising the synthesis of the porphyrin ring through dipyrromethane followed by functionalisation of the porphyrin with aliphatic or aromatic amino or ammonium groups, and possible complexation with the metal cation if the metal complex is required.

Some examples of the above said processes are illustrated in the following schemes.

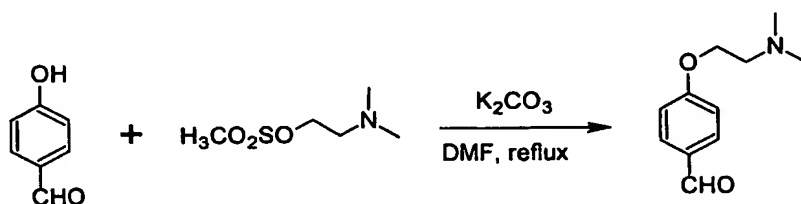
SCHEME 1: Synthesis of compounds of formula (I) in which $R = R_2 = R_3$

SCHEME 1A: pre-functionalization of suitable reagents (selected so to form the porphyrin ring) with amino groups, followed by statistical synthesis of the porphyrin ring, and possible modification of the amino groups in ammonium groups

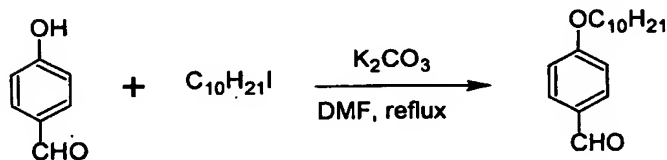
5



10

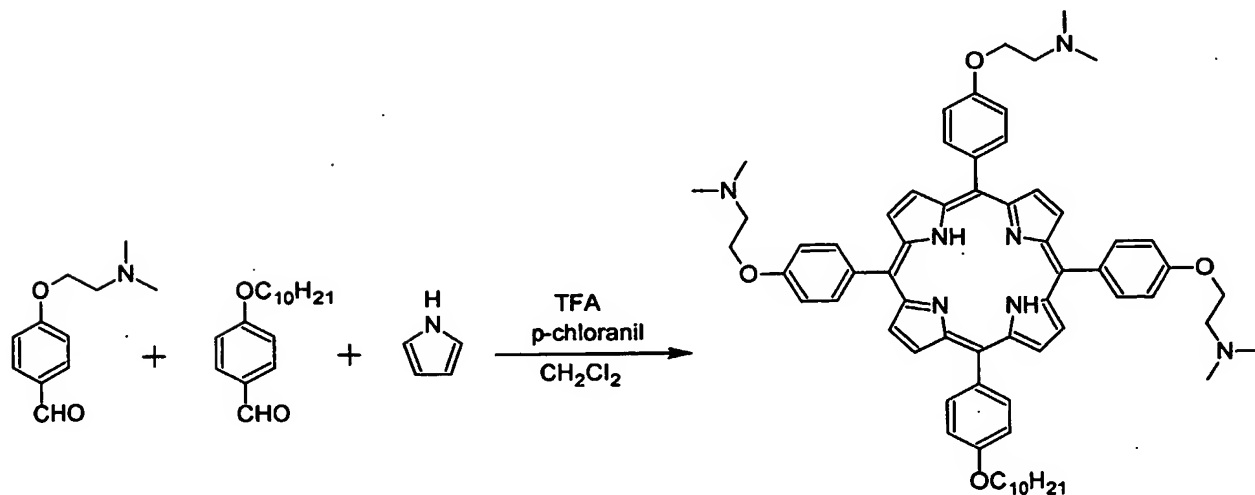


15

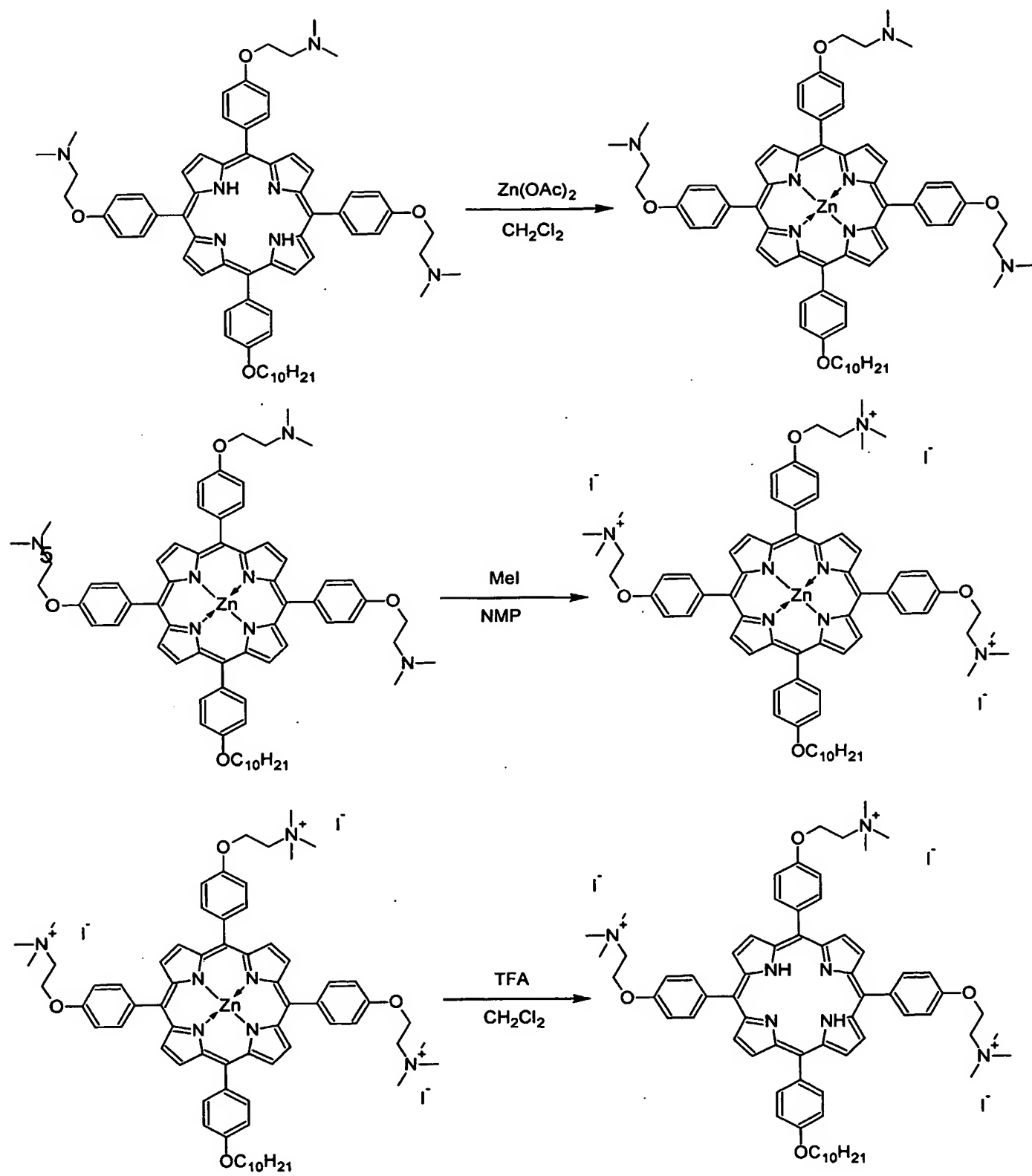


20

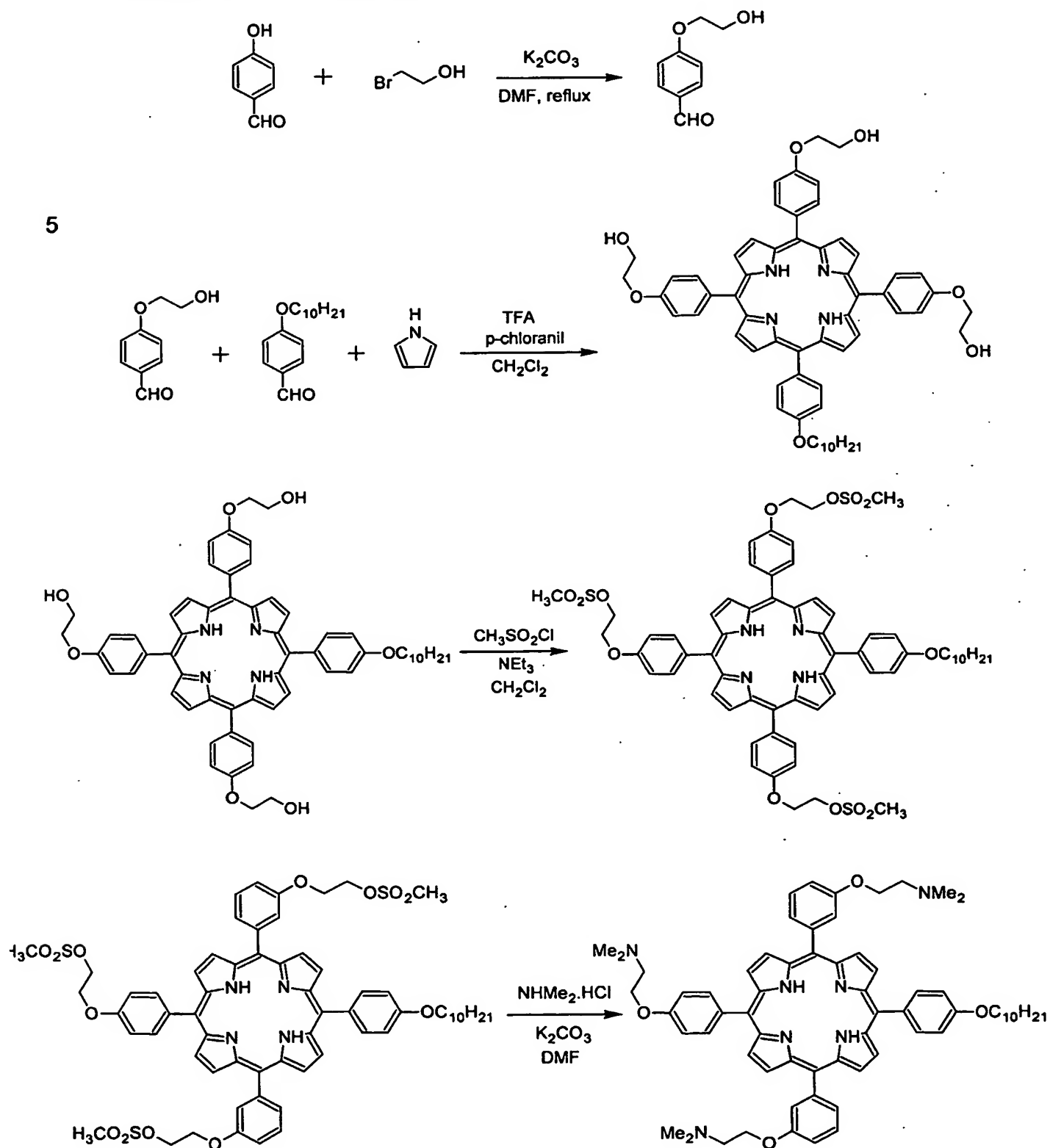
25

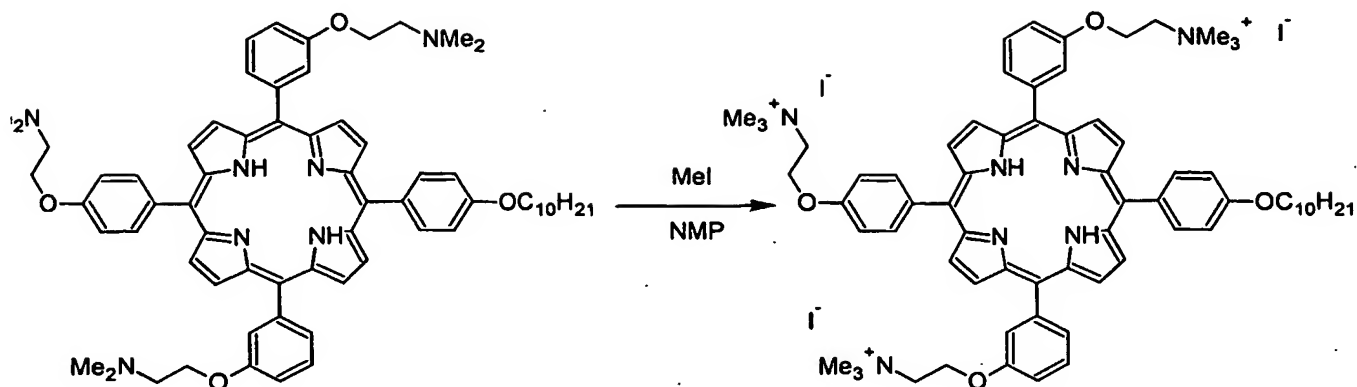


30

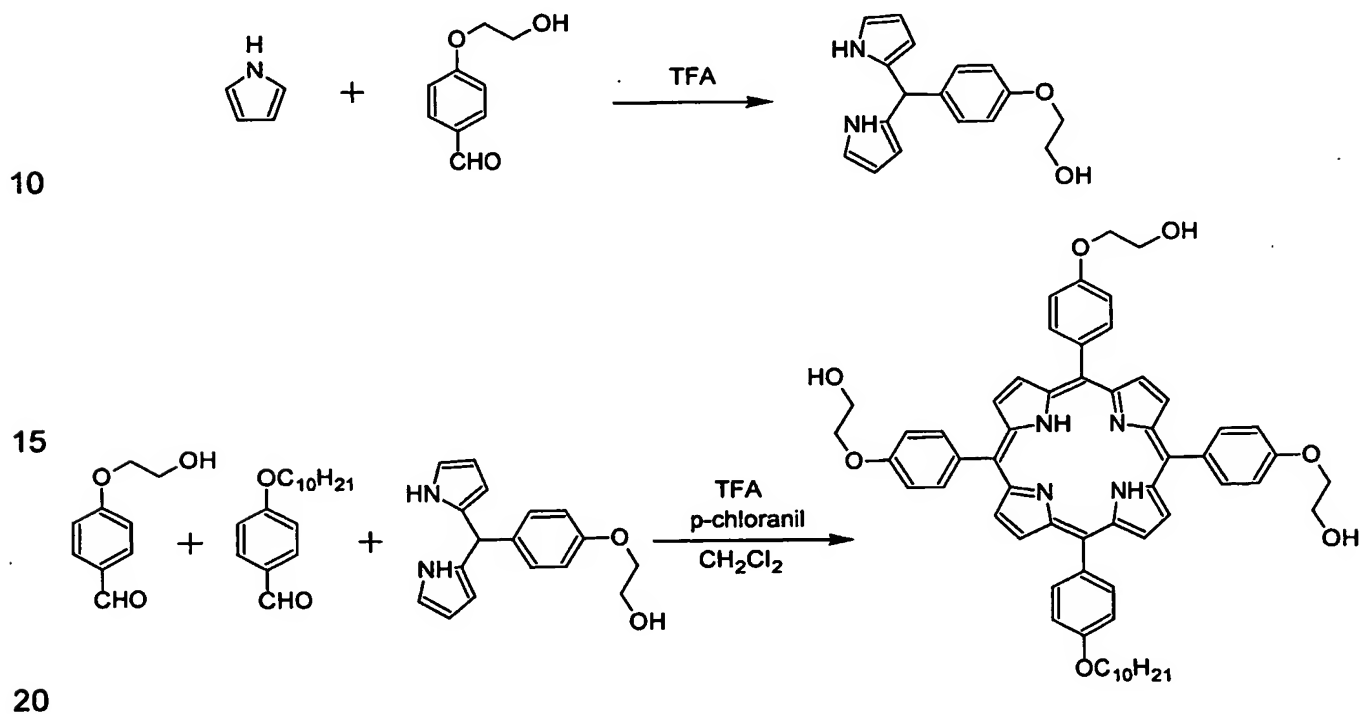


SCHEME 1B: statistical synthesis with formation of the porphyrin ring followed by functionalization of the porphyrin with the present amino or ammonium groups





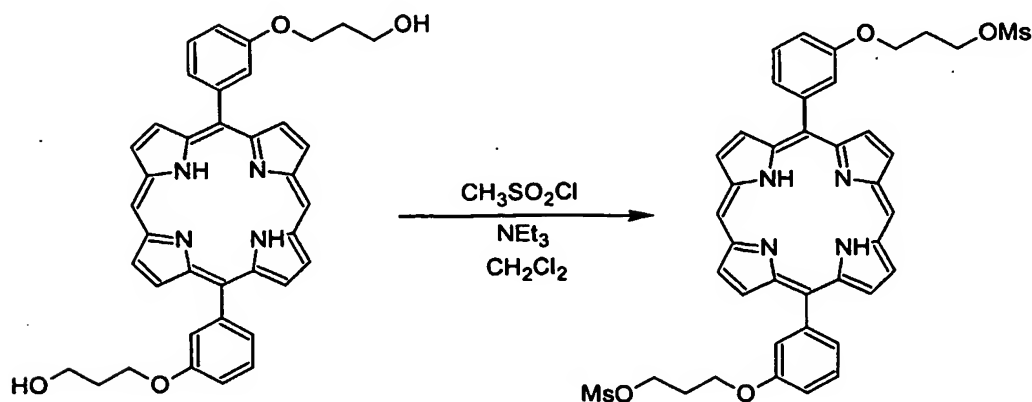
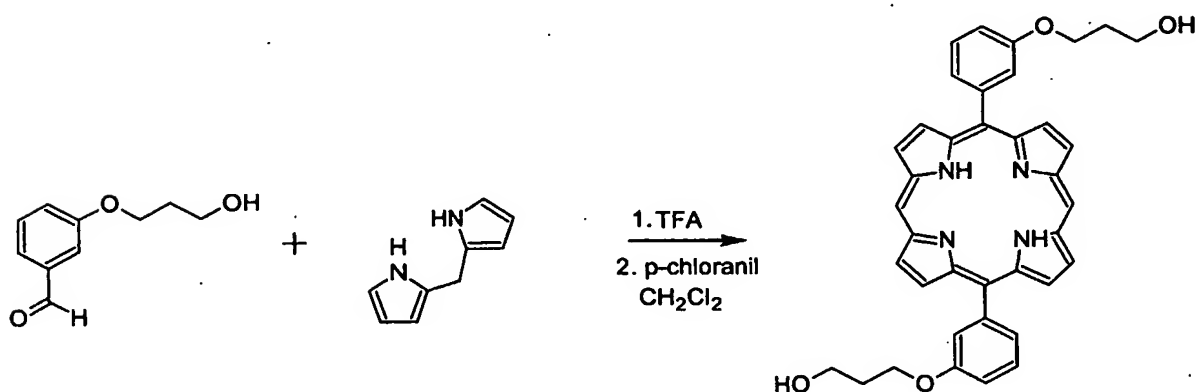
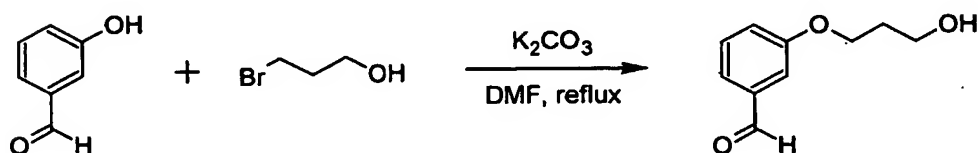
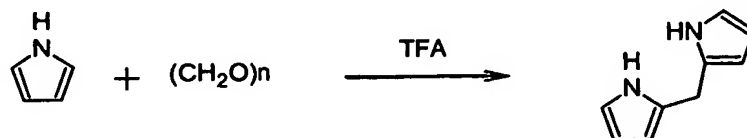
SCHEME 1C: synthesis of the porphyrin ring through suitable dipyrromethane derivatives followed by functionalisation of the porphyrin with the present amino or ammonium groups

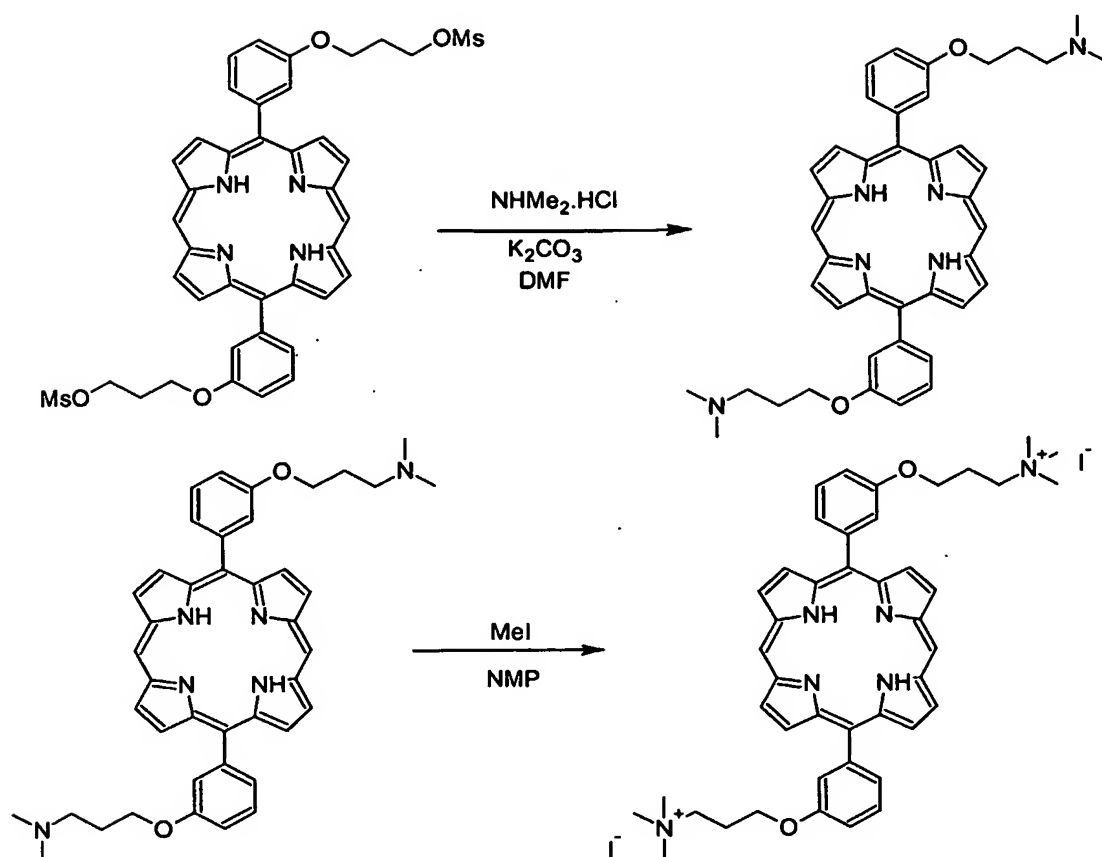


The so-obtained porphyrin derivatives can be further processed to obtain the present compounds of formula (I) for example according to the last three steps in the above Scheme 1B.

SCHEME 2: Synthesis of compounds in which $R = R_2$ and $R_1 = R_3$

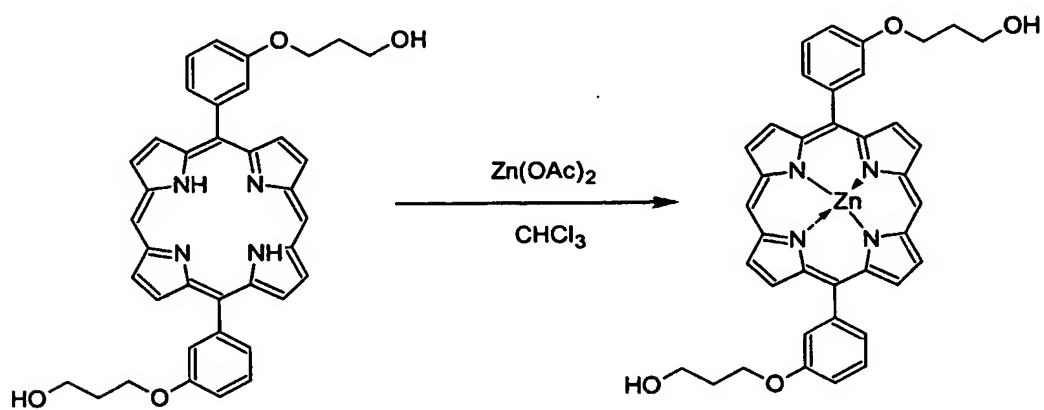
SCHEME 2A: synthesis of the porphyrin ring through dipyrromethane followed by functionalisation of the porphyrin with aliphatic amino or ammonium groups

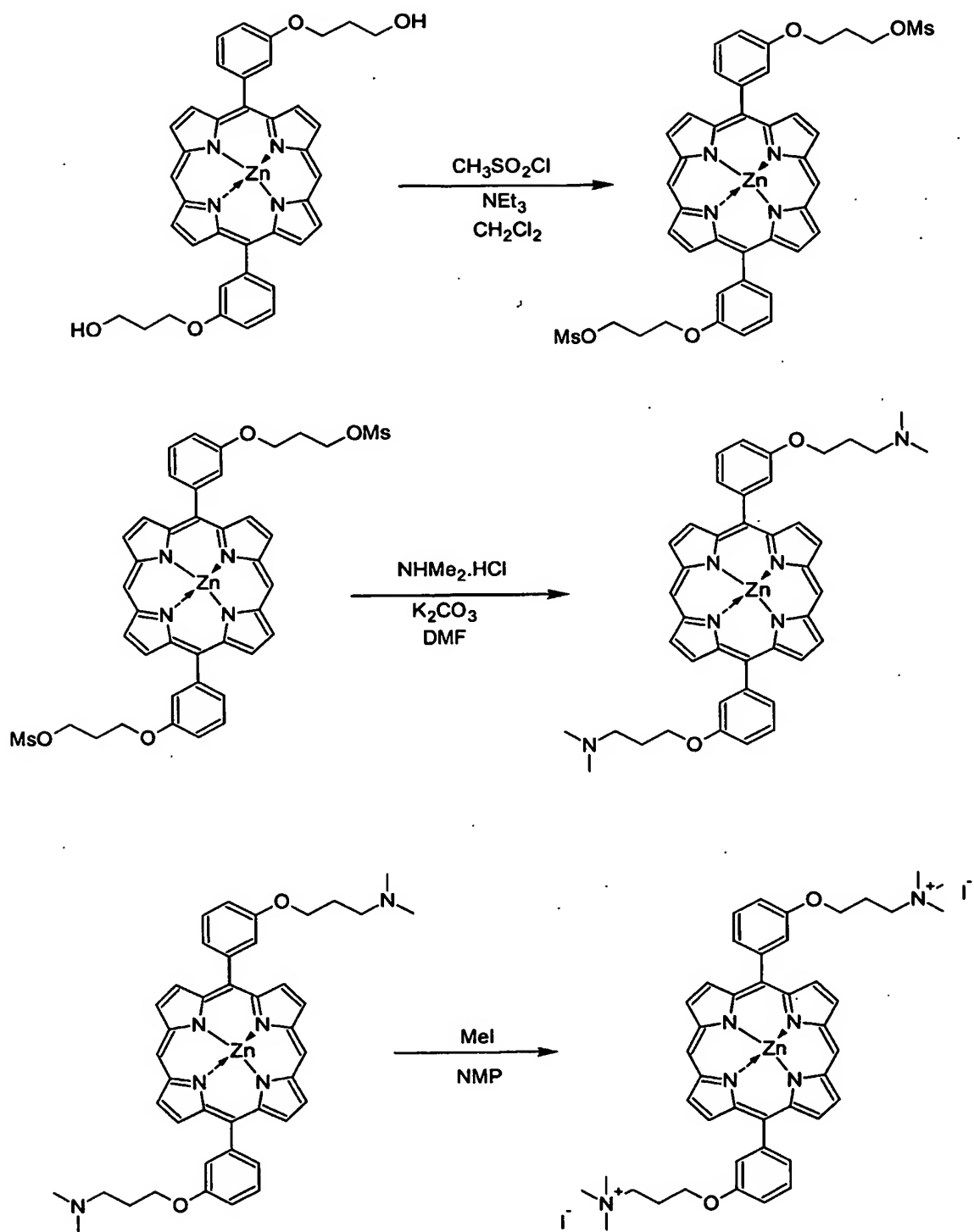




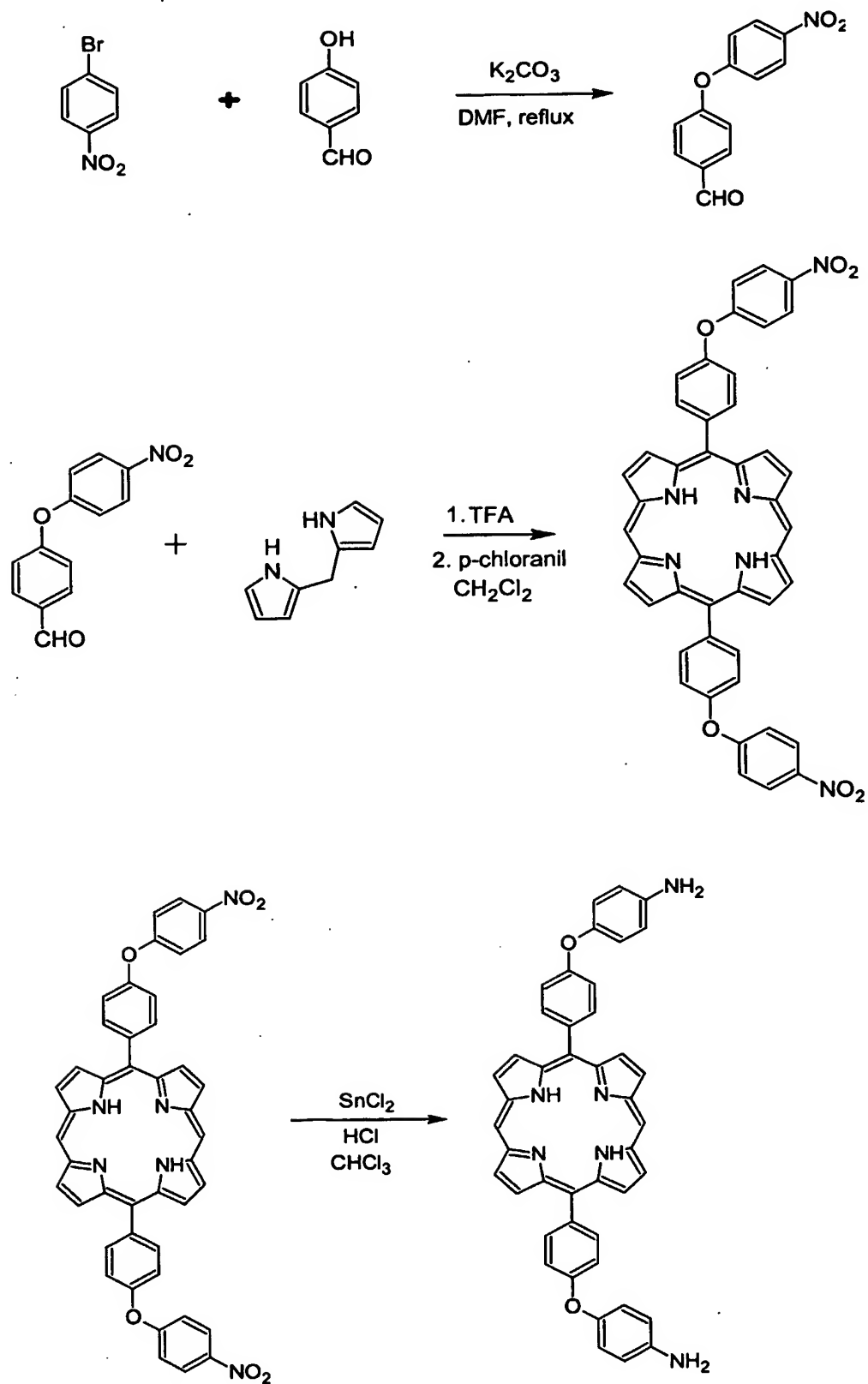
SCHEME 2B: preparation of Zn(II)-porphyrinates bearing aliphatic amino/ammonium groups starting from the corresponding porphyrins bearing aliphatic hydroxy groups

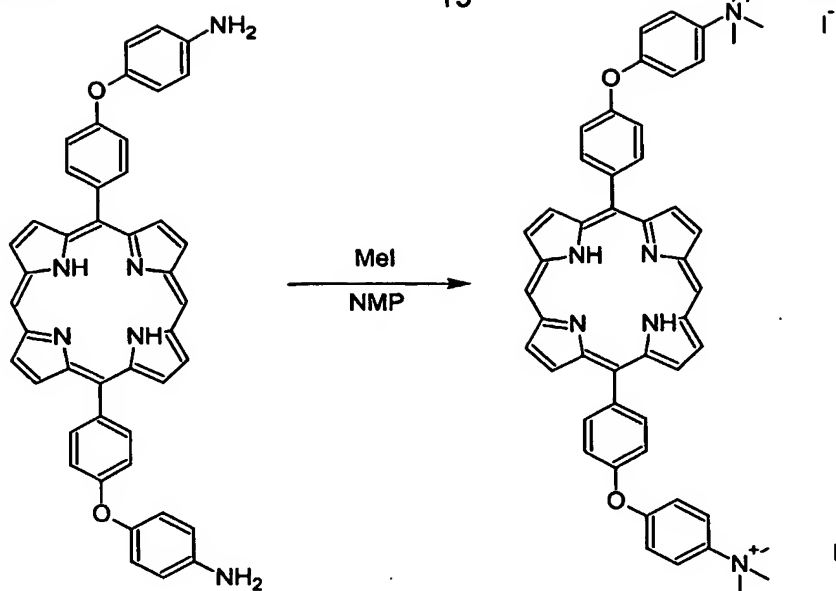
5





SCHEME 2C: preparation of porphyrins bearing aromatic amino/ammonium groups





The present porphyrins can be converted in the corresponding metal complexes by treatment with the suitable metal cation according to well-known procedures in organic chemistry. The introduction of the metal cation into the porphyrin ring may be achieved before or after the functionalisation of the porphyrin ring with the present amino or ammonium groups.

All the quaternary ammonium porphyrin iodides derivatives prepared can be easily converted in the corresponding chlorides or other more acceptable salts for biological purposes.

The compounds of the present invention have been prepared according to the procedure described above, identified and characterised by spectroscopic (¹H-NMR, ¹³C-NMR), spectrophotometric (UV-Vis), and spectrometric (EI, ESI or DCI-MS) analytical techniques.

The following examples are given to provide a non limiting illustration of the invention.

EXAMPLE 1

Synthesis of 5,10,15-tris-[4-(2-N,N,N-trimethylammoniummethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide by statistical synthesis with pre-functionalization

Step a) Synthesis of N,N-dimethyl-2-methylsulphonylethylamine

To a solution of N,N-dimethylethanolamine (890 mg, 10 mmol) and triethylamine (1520 mg, 15 mmol) in anhydrous CH₂Cl₂, kept under nitrogen atmosphere, at 0°C, methansulphonyl chloride (1220 mg, 11 mmol) was added. The mixture was

kept under stirring and at 0°C for 1 hour, and then concentrated by evaporation. The residue was dissolved in CH₂Cl₂, washed with Na₂CO₃ saturated solution and with deionized water. The organic phase was dried under Na₂SO₄ and the solvent removed by evaporation. The product was used as obtained, without purification,

5 for the following step b) (1330 mg, yield 80%).

¹H-NMR: (300 MHz, DMSO-d₆) 3.51 (2H, t, J=5.8 Hz), 3.03 (6H, s), 3.00 (2H, t, J=5.8 Hz), 2.71 (6H, s)

EI-MS: 167.23 Th [C₅H₁₃NO₃S]⁺

Step b) Synthesis of 4-(N,N-dimethylaminoethoxy)benzaldehyde

10 To a solution of 4-hydroxybenzaldehyde (500 mg, 4 mmol) and K₂CO₃ (662 mg, 4.8 mmol) in anhydrous DMF, N,N-dimethyl-2-metilsulphonylethylamine (775 mg, 4.4 mmol) was added. The reaction mixture was heated to reflux, under magnetic stirring, for 4 hours, then poured in water to obtain a suspension from which the solid was isolated by filtration. The crude product was purified by chromatography

15 on silica gel (ethyl acetate), to give 379 mg of pure product of the title (yield 49%).

¹H-NMR: (300 MHz, DMSO-d₆): 9.86 (1H, s), 8.78 (2H, d, J=8.8 Hz), 6.98 (2H, d, J=8.8 Hz), 3.28 (2H, t, 5.5 Hz), 2.97 (2H, t, J=5.5 Hz), 2.71 (6H, s)

EI-MS: 193.25 Th [C₁₁H₁₅NO₂]⁺

Step c) Synthesis of 4-decyloxybenzaldehyde

20 To a solution of 4-hydroxybenzaldehyde (732 mg, 6 mmol) in anhydrous DMF (13ml), under nitrogen atmosphere, K₂CO₃ (1658 mg, 12 mmol), and, after 10 minutes, iododecane (1785 mg, 7.2 mmol) were added. The mixture was heated to reflux for 3 hours, then water was added and the product was extracted with CH₂Cl₂. The organic layers were washed with water and with NaCl saturated
25 solution, dried with Na₂SO₄. After evaporation of the solvent, the crude product was purified by chromatography on silica gel (Petroleum ether/Ethyl acetate 11/1) and 1530 mg (yield 97%) of the pure product of the title were obtained.

¹H NMR (300 MHz, DMSO-d₆): 9.84 (1H, s), 7.82 (2H, d, J = 9 Hz), 7.09 (2H, d, J = 9 Hz), 4.06 (2H, t, J = 6.6 Hz), 1.71 (2H, tt, J = 6.6 Hz, 6.5 Hz), 1.30 (14H, m),
30 0.83 (3H, t, 6.5 Hz).

¹³C NMR (75 MHz, DMSO-d₆): 191.7, 164.2, 132.2, 130.0, 115.3, 68.4, 31.7, 29.4, 29.4, 29.2, 29.1, 28.9, 25.8, 22.5, 14.3.

5 EI-MS: 262.3 Th [C₁₇H₂₆O₂]⁺

Step d) Synthesis of 5,10,15-tris-[4-(2-N,N-dimethylaminoethoxy)phenyl]-[20-(4-decyloxy)phenyl]porphyrin

To a solution of 4-decyloxybenzaldehyde coming from step c) (505 mg, 2 mmol),
5 4-(N,N-dimethylaminoethoxy)benzaldehyde prepared as described in step b)
(1160 mg, 6 mmol) and pyrrole (537 mg, 8 mmol) in anhydrous CH₂Cl₂,
trifluoroacetic acid (570 mg, 6.7 mmol) was added and the mixture was kept under
magnetic stirring, at room temperature, under nitrogen atmosphere, for 20 hours.
Then *p*-chloranil (1650 mg, 6.7 mmol) was added and the final mixture stirred for
10 additional 4 hours. Work-up: washing with Na₂CO₃ saturated solution, drying on
Na₂SO₄, and removing solvent by evaporation. The crude product was finally
purified by reverse phase chromatography on C18 silica gel (water/acetonitrile
3/1), to give 245 mg of the title product (yield 12%).

¹H NMR (300 MHz, CDCl₃): 8.85 (8H, m), 8.11 (8H, m), 7.29 (8H, m), 4.40 (6H, t, J
15 = 5.6 Hz), 4.25 (2H, t, J = 6.3 Hz), 2.99 (6H, t, J = 5.6 Hz), 2.53 (18H, s), 1.97 (2H,
tt, J = 7.2 Hz), 1.65-1.32 (14H, m), 0.91 (3H, t, J = 6.6 Hz); -2.77 (2H, s).

¹³C NMR (75 MHz, CDCl₃, selected data): 163.4, 163.0, 161.8, 135.6, 131.1,
118.0, 112.7, 77.2, 68.3, 66.8, 58.1, 49.1, 44.4, 37.7, 31.9, 29.6, 29.4, 29.3, 26.2,
22.6, 14.0.

20 ESI-MS: m/z 1032.5 Th [C₆₆H₇₈N₇O₄]⁺.

Step e) Synthesis of 5,10,15-tris-[4-(2-N,N-dimethylaminoethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrinate zinc (II)

To a solution of 5,10,15-tris-4-(2-N,N-dimethylaminoethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin coming from step d) (40 mg, 0.04 mmol) in CHCl₃,
25 ZnOAc₂ (3.7 mg, 0.02 mmol) was added. The reaction mixture was kept under
magnetic stirring, at room temperature, for 30 minutes, then filtered in vacuum and
the liquid phase concentrated by evaporation to give 34.7 mg of the desired
product of the title (yield 80%).

¹H-NMR: (300 MHz, DMSO-d₆): 8.92-8.77 (6H, m), 8.81-8.68 (2H, m), 8.23-8.17
30 (6H, m), 8.10 (2H, d, J = 8.7 Hz), 7.84 (2H, d, J = 8.7 Hz) 7.90-7.81 (6H, m), 3.66
(2H, m), 3.40 (2H, t, J = 5.8 Hz), 2.95 (2H, t, J=5.5 Hz), 2.68 (6H, s), 2.01-0.80
(9H, m)

ESI-MS: 1094.5 Th $[C_{66}H_{76}N_7O_4Zn]^+$

Step f) Synthesis of 5,10,15-tris-[4-(2-N,N,N-trimethylammoniumethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrinate zinc (II) triiodide

To a solution of 5,10,15-tris-[4-(2-N,N-dimethylaminoethoxy)-phenyl]-20-[(4-decyloxy)phenyl]porphyrinate zinc (II) coming from step e) (20 mg, 0.02 mmol) in dry NMP, iodomethane (0.6 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 8 hours, and then diethyl ether was added slowly until a precipitate appeared. The suspension was filtered and the solid re-crystallised from $CHCl_3$ /diethyl ether to give 22.9 mg of pure product of the title (yield 75%).

1H -NMR: (300 MHz, $DMSO-d_6$): 8.90-8.72 (6H, m), 8.81-8.65 (2H, m), 8.26-8.12 (6H, m), 8.15 (2H, d, $J = 8.7$ Hz), 7.84 (2H, d, $J = 8.7$ Hz) 7.80-7.74 (6H, m), 3.66 (2H, m), 4.30 (2H, t, $J = 5.6$ Hz), 2.95 (2H, t, $J = 5.5$ Hz), 3.43 (6H, s), 2.07-0.75 (9H, bm)

ESI-MS: m/z 379.5 Th $[C_{69}H_{84}N_7O_4Zn]^{3+}$

Step g) Synthesis of 5,10,15-tris-[4-(2-N,N,N-trimethylammoniumethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide

To a solution in $CHCl_3$ of 5,10,15-tris-[4-(2-N,N,N-trimethylammoniumethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrinate zinc (II) triiodide coming from step f) (30 mg, 0.02 mmol) TFA was added. The mixture was kept at room temperature for 20 minutes, then filtered through K_2CO_3 , and the solvent removed by evaporation, to give 26.3 mg of product of the title (yield 90%).

1H NMR (300 MHz, CD_3OD): 8.86 (8H, m), 8.49 (8H, m), 7.69 (6H, m), 7.57 (2H, m), 4.91 (6H, m), 4.35 (2H, t, $J = 6$ Hz), 4.11 (6H, m), 3.46 (27H, s), 2.00 (2H, m), 1.67 (2H, $J = 6$ Hz), 1.56-1.28 (12H, m), 0.92 (3H, t, $J = 6.6$ Hz).

^{13}C NMR (75 MHz, CD_3OD , selected data): 149.5, 140.3, 134.7, 130.0, 114.4, 112.7, 98.8, 68.4, 65.5, 62.5, 53.8, 31.9, 29.6, 29.5, 29.4, 29.3, 26.1, 22.5, 13.2.

ESI-MS: m/z 358.8 Th $[C_{69}H_{86}N_7O_4]^{3+}$.

EXAMPLE 2

Synthesis of 5,10,15-tris-[4-(2-N,N,N-trimethylammoniumethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide by statistical synthesis with functionalization on the porphyrin

Step a) Synthesis of 4-(2-hydroxyethoxy)benzaldehyde

To a solution of 4-hydroxybenzaldehyde (366 mg, 3 mmol) in anhydrous DMF (7ml), under nitrogen atmosphere, K_2CO_3 (829 mg, 6 mmol), and, after 10 minutes, bromoethanol (450 mg, 3.6 mmol) were added. The mixture was heated to reflux for 3 hours, then water was added and the product was extracted with CH_2Cl_2 . The organic layers were washed with water and with NaCl saturated solution, dried with Na_2SO_4 . After evaporation of the solvent, the crude product was purified by chromatography on silica gel (Petroleum ether/Ethyl acetate 2/1); 400 mg (yield 80%) of pure product of the title were obtained.

1H NMR (300 MHz, $DMSO-d_6$): 9.85 (1H, s), 7.84 (2H, d, $J = 8.7$ Hz), 7.12 (2H, d, $J = 8.7$ Hz), 4.87 (1H, t, $J = 5.1$ Hz), 4.10 (2H, dt, $J = 5.1$ Hz, 4.8 Hz), 3.73 (1H, t, $J = 4.8$ Hz).

^{13}C NMR (75 MHz, $DMSO-d_6$): 191.7, 164.2, 132.2, 130.0, 115.4, 70.5, 59.8.

Step b) Synthesis of 5,10,15-tris-[4-(2-hydroxyethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin

To a solution of 4-decyloxybenzaldehyde (190 mg, 0.72 mmol), 4-(2-hydroxyethoxy)benzaldehyde (360 mg, 2.17 mmol) and pyrrole (241 mg, 3.6 mmol) in dry CH_2Cl_2 , trifluoroacetic acid (228 mg, 2 mmol) was added and the mixture was kept under magnetic stirring, at room temperature, under nitrogen atmosphere, for 4 hours. Then *p*-chloranil (492 mg, 2 mmol) was added and the final mixture stirred for additional 15 hours, then the organic phase was washed with Na_2CO_3 saturated solution, dried on Na_2SO_4 and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel (THF/petroleum ether 1/1 + 1% TEA, to THF + 1% TEA), to give 75 mg of the title product (yield 10%).

1H NMR (300 MHz, $CDCl_3$): 8.87 (8H, m), 8.10 (8H, m), 7.27 (8H, m), 4.37 (6H, t, $J = 4.2$ Hz), 4.21 (3H, m), 4.15 (8H, m); 1.96 (2H, tt, $J = 7.5$ Hz), 1.57-1.25 (14H, m), 0.90 (3H, t, $J = 6.9$ Hz); -2.76 (2H, s).

^{13}C NMR (75 MHz, $CDCl_3$, selected data): 159.0, 158.4, 135.6, 135.1, 134.3, 131.0, 120.0, 119.6, 112.7, 77.2, 69.4, 68.3, 61.6, 31.9, 29.6, 29.6, 29.5, 29.4, 29.3, 26.2, 22.6, 14.1.

ESI-MS: m/z 951.2 Th $[C_{60}H_{63}N_4O_7]^+$.

Step c) Synthesis of 5,10,15-tris-[4-(2-methylsulphonylethoxy)phenyl]-20-(4-decyloxy)phenyl]porphyrin

To a solution of 5,10,15-tris-[4-(2-hydroxyethoxy)phenyl]-20-(4-decyloxy)phenyl]porphyrin (70 mg, 0.073 mmol) in anhydrous CH_2Cl_2 , under nitrogen atmosphere, at 0°C , triethylamine (73 mg, 0.73 mmol) and methansulphonyl chloride (42 mg, 0.37 mmol) were added. The mixture was kept under magnetic stirring at room temperature for 3 hours, then washed with NaHCO_3 saturated solution and with water. The organic phase was dried with Na_2SO_4 and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50/1), to obtain 65 mg of the title product (yield 65%).

^1H NMR (300 MHz, CDCl_3): 8.87 (8H, m), 8.12 (8H, m), 7.29 (8H, m), 4.77 (6H, t, $J = 4.5$ Hz), 4.54 (6H, t, $J = 4.5$ Hz), 4.25 (2H, t, $J = 6$ Hz), 3.24 (9H, s), 1.96 (2H, tt, $J = 8$ Hz), 1.61-1.25 (14H, m), 0.91 (3H, t, $J = 7$ Hz); -2.77 (2H, s).

^{13}C NMR (75 MHz, CDCl_3 , selected data): 159.0, 157.8, 140.3, 135.6, 135.6, 134.2, 130.9, 120.2, 119.4, 114.5, 112.8, 77.2, 68.3, 66.2, 66.1, 37.9, 31.9, 29.6, 29.6, 29.5, 29.3, 26.2, 22.6, 14.1.

ESI-MS: m/z 1185.1 Th $[\text{C}_{63}\text{H}_{69}\text{N}_4\text{O}_{13}\text{S}_3]^+$.

Step d) Synthesis of 5,10,15-tris-[4-(2-N,N-dimethylaminoethoxy) phenyl]-20-(4-decyloxy)phenyl]porphyrin

To a solution of 5,10,15-tris-[4-(2-methylsulphonylethoxy)phenyl]-20-(4-decyloxy)phenyl]porphyrin (65 mg, 0.055 mmol) in anhydrous DMF (5ml), under nitrogen atmosphere, K_2CO_3 (46 mg, 0.33 mmol), and, after 10 minutes, dimethylamine hydrochloride (27 mg, 0.055 mmol) were added. The mixture was heated at 80°C for 20 hours, then water was added and the product was extracted with CH_2Cl_2 . The organic layers were washed with water and with NaCl saturated solution, then dried with Na_2SO_4 . After evaporation the crude product was purified by chromatography on silica gel (THF to THF/DMF 4/1). After the chromatography, the product was re-crystallized from $\text{CHCl}_3/\text{Petroleum Ether}$ 1/1 and 26 mg (yield 50%) of the title product were obtained.

^1H NMR (300 MHz, CDCl_3): 8.85 (8H, m), 8.11 (8H, m), 7.29 (8H, m), 4.40 (6H, t, $J = 5.6$ Hz), 4.25 (2H, t, $J = 6.3$ Hz), 2.99 (6H, t, $J = 5.6$ Hz), 2.53 (18H, s), 1.97 (2H, tt, $J = 7.2$ Hz), 1.65-1.32 (14H, m), 0.91 (3H, t, $J = 6.6$ Hz); -2.77 (2H, s).

^{13}C NMR (75 MHz, CDCl_3 , selected data): 163.4, 163.0, 161.8, 135.6, 131.1,
5 118.0, 112.7, 77.2, 68.3, 66.8, 58.1, 49.1, 44.4, 37.7, 31.9, 29.6, 29.4, 29.3, 26.2, 22.6, 14.0.

UV-VIS (DMF): λ_{max} 651, 555, 518, 430, 408, 264, 245, 235.

ESI-MS: m/z 1032.5 Th $[\text{C}_{66}\text{H}_{78}\text{N}_7\text{O}_4]^+$.

Step e) Synthesis of 5,10,15-tris-[4-(2-N,N,N-trimethylammonium)ethoxyphenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide

To a solution of 5,10,15-tris-[4-(2-N,N-dimethylaminoethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin (15 mg, 0.015 mmol) in dry NMP (5 ml), iodomethane (100 mg, 0.6 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 20 hours, then diethyl ether was added slowly
15 until a precipitate appeared. The suspension was filtered and the solid crystallized from MeOH/diethyl ether to give 20 mg of pure product of the title (yield 94%).

^1H NMR (300 MHz, $\text{DMSO}-d_6$): 8.16 (6H, m), 8.08 (2H, m), 7.45 (6H, m), 7.35 (2H, m), 4.76 (6H, m), 4.25 (2H, t, $J = 6$ Hz), 3.97 (6H, m), 3.32 (27H, s), 1.88 (2H, m), 1.56-1.28 (14H, m), 0.86 (3H, t, $J = 6.3$ Hz); -2.91 (2H, s).

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, selected data): 158.0, 136.1, 134.9, 131.9, 120.1,
20 113.9, 113.7, 68.3, 65.0, 62.55, 53.9, 31.9, 29.6, 29.5, 29.4, 29.3, 26.2, 22.7, 14.5.

UV-VIS (DMF): λ_{max} 650, 554, 517, 431, 400, 254, 245, 234.

ESI-MS: m/z 358.8 Th $[\text{C}_{69}\text{H}_{86}\text{N}_7\text{O}_4]^{3+}$.

Step b1) Synthesis of 2-[4-(di-1H-pyrrol-2-ylmethyl)phenoxy]ethanol

To a solution of 4-(2-hydroxyethoxy)benzaldehyde (664 mg, 4 mmol) in pyrrole (12.5 ml, 180 mmol), TFA (114 mg, 1 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 1 hour, then ethyl acetate (200 ml) was added and the solution washed with NaHCO_3 saturated solution, then the organic phase was dried with Na_2SO_4 . After evaporation, the crude
30 product was purified by chromatography (Petroleum ether/Ethyl acetate 1/1). 811 mg (yield 72%) of the title product were obtained.

¹H NMR (300 MHz, CDCl₃): 7.94 (2H, bs), 7.13 (2H, m), 6.87 (2H, m), 6.69 (2H, m), 6.15 (2H, m), 5.91 (2H, m), 5.91 (1H, s), 4.07 (2H, dt, J = 9, 4.5 Hz), 3.95 (2H, dt, J = 9, 7.5 Hz).

¹³C NMR (75 MHz, CDCl₃): 157.6, 134.7, 132.7, 129.5, 117.1, 114.6, 108.4, 107.0, 69.1, 61.4, 43.1.

Step c1) Synthesis of 5,10,15-tris-[4-(2-hydroxyethoxy)phenyl]-20-[(4-decyloxy)phenyl]porphyrin

To a solution of 2-[4-(di-1*H*-pyrrol-2-ylmethyl) phenoxy]ethanol (620 mg, 2.2 mmol, 4-decyloxybenzaldehyde (262 mg, 1 mmol) and 4-(2-hydroxyethoxy)benzaldehyde (166 mg, 1.4 mmol) in dry CH₂Cl₂, trifluoroacetic acid (114 mg, 1 mmol) was added and the mixture was kept under magnetic stirring, at room temperature, under nitrogen atmosphere, for 4 hours. Then *p*-chloranil (492 mg, 2 mmol) was added and the final mixture stirred for additional 15 hours, then the organic phase was washed with Na₂CO₃ saturated solution, dried on Na₂SO₄ and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel (THF/Petroleum ether 1/1 + 1% TEA, to THF + 1% TEA), to give 35 mg of title product (yield 3.7%).

According to the procedures described in Examples 1 or 2 the following porphyrins have been prepared:

EXAMPLE 3

5,10,15-tris-[4-(N-methylpiperidin-4-yl)oxy]phenyl)-20-[(4-decyloxy)phenyl]porphyrin

ESI-MS: m/z 1110.5 Th [C₇₂H₈₄N₇O₄]⁺

EXAMPLE 4

5,10,15-tris-[4-(N,N-dimethylpiperidin-4-ium)oxy]phenyl)-20-[(4-decyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 385.2 Th [C₇₅H₉₂N₇O₄]³⁺

EXAMPLE 5

5,10,15-tris-[3-(2-morpholin-4-ylethoxy)phenyl]-20-[(4-decyloxy)phenyl] porphyrin

ESI-MS: m/z 1158.8 Th [C₇₂H₈₄N₇O₇]⁺

EXAMPLE 6

5,10,15-tris-[[3-(2-methylmorpholin-4-ium)ethoxy]phenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 400.9 Th [C₇₅H₉₂N₇O₇]³⁺

EXAMPLE 7

5 5,10,15-tris-[4-[4-(N,N-dimethylamino)phenoxy]phenyl]-20-[(4-decyloxy)phenyl]porphyrin

ESI-MS: m/z 1176.6 Th [C₇₈H₇₈N₇O₄]⁺

EXAMPLE 8

10 5,10,15-tris-[4-[4-(N,N,N-trimethylammonium)phenoxy]phenyl]-20-[(4-decyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 406.8 Th [C₈₁H₈₆N₇O₄]³⁺

EXAMPLE 9

5,10,15-tris-[4-[3-(N,N-dimethylamino)phenyl]thiophenyl]-20-[(3-undecyloxy)phenyl]porphyrin

15 ESI-MS: m/z 1239.7 Th [C₇₉H₈₀N₇OS₃]⁺

EXAMPLE 10

5,10,15-tris-[4-[3-(N,N,N-trimethylammonium)phenyl]thiophenyl]-20-[(4-undecyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 427.7 Th [C₈₂H₈₈N₇OS₃]³⁺

20 EXAMPLE 11

5,10,15-tris-[3-(3-N,N-dimethylaminopropoxy)phenyl]-20-[(3-undecyloxy)phenyl]porphyrin

ESI-MS: m/z 1088.6 Th [C₇₀H₈₆N₇O₄]⁺

EXAMPLE 12

25 5,10,15-tris-[3-(3-N,N,N-trimethylammoniumpropoxy)phenyl]-20-[(3-undecyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 377.7 Th [C₇₃H₉₄N₇O₄]³⁺

EXAMPLE 13

5,10,15-tris-[4-[4-(N,N-dimethylamino)butoxy]phenyl]-20-[(4-undecyloxy)phenyl]porphyrin

30

ESI-MS: m/z 1131.6 Th [C₇₃H₉₂N₇O₄]⁺

EXAMPLE 14

5,10,15-tris-{4-[4-(N,N,N-trimethylammonium)butoxy]phenyl}-20-[(4-undecyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 379.7 Th [C₇₆H₁₀₀N₇O₄]³⁺

EXAMPLE 15

5 5-{4-[2,4,6-tris-[(dimethylamino)methyl]phenoxy]phenyl}-10,15,20-tris-[(4-decyloxy)phenyl]porphyrin

ESI-MS: : m/z 1346.9 Th [C₈₉H₁₁₆N₇O₄]⁺

EXAMPLE 16

10 5-{4-[2,4,6-tris-[(trimethylammonium)methyl]phenoxy]phenyl}-10,15,20-tris-[(4-decyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 463.6 Th [C₉₂H₁₂₄N₇O₄]³⁺

EXAMPLE 17

5-{3-[2-(dimethylamino)]-1-[[dimethylamino)methyl]ethoxy}phenyl}-10,15,20-tris-[(3-decyloxy)phenyl]porphyrin

15 ESI-MS: m/z 1227.8 Th [C₈₁H₁₀₇N₆O₄]⁺

EXAMPLE 18

5-{3-[2-(trimethylammonium)]-1-[[trimethylammonium)methyl]ethoxy}phenyl}-10,15,20-tris-[(3-decyloxy)phenyl]porphyrin diiodide

ESI-MS: m/z 628.4 Th [C₈₃H₁₁₂N₆O₄]²⁺

20 EXAMPLE 19

5,10,15-tris-{4-[3-(diethylamino)propoxy]phenyl}-20-[(4-decyloxy)phenyl] porphyrin

ESI-MS: m/z 1172.7 Th [C₇₆H₉₈N₇O₄]⁺

EXAMPLE 20

5,10,15-tris-{4-[3-(trimethylammonium)propoxy]phenyl}-20-[(4-decyloxy)phenyl]

25 porphyrin triiodide

ESI-MS: m/z 419.6 Th [C₈₂H₁₁₂N₇O₄]³⁺

EXAMPLE 21

5,10,15-tris-{4-(2-aminoethoxy)phenyl}-20-[(4-decyloxy)phenyl] porphyrin

ESI-MS: m/z 962.5 Th [C₈₁H₆₈N₇O₄]⁺

30 EXAMPLE 22

5,10,15-tris-{4-(2-trimethylammonium)ethoxy]phenyl}-20-[(4-decyloxy)phenyl]porphyrin triiodide

ESI-MS: m/z 363.5 Th [C₇₀H₈₈N₇O₄]³⁺

EXAMPLE 23

5,10,15-tris-{{[4-(N,N,N-trimethylammonium)phenoxy]carbonyl}phenyl}-20-[(4-decyloxy) phenyl]porphyrin triiodide

5 ESI-MS: m/z 434.6 Th [C₈₄H₈₆N₇O₇]³⁺

EXAMPLE 24

5-{4-{{2-(trimethylammonium)-1-[(trimethylammonium)methyl]ethoxy}carbonyl}phenyl}-10,15,20-tris-[(3-decyloxy)phenyl]porphyrin diiodide

ESI-MS: m/z 1270.8 Th [C₈₃H₁₁₀N₆O₅]⁺

10 EXAMPLE 25

Synthesis of 5,15-bis-[3-(3-N,N,N-trimethylammoniumpropoxy)phenyl] porphyrin diiodide

Step a) Synthesis of 2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (dipyrromethane)

To a solution of *p*-formaldehyde (1100 mg, 35 mmol) in pyrrole (50 ml, 720 mmol),
15 at 50°C, TFA (416 mg, 3.5 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 30 minutes, then ethyl acetate was added and the solution washed with NaHCO₃ saturated solution, then the organic phase was dried on Na₂SO₄. After evaporation the crude product was purified by chromatography on silica gel (Petroleum Ether/Ethyl acetate 4/1 + 1% TEA). 1950
20 mg (yield 38%) of the product were obtained.

¹H NMR (300 MHz, DMSO-d₆): 6.55 (2H, m), 5.85 (2H, m), 5.71 (2H, m), 3.78 (2H, s).

¹³C NMR (75 MHz, CDCl₃): 129.0, 117.3, 108.3, 106.4, 26.2.

Step b) Synthesis of 3-(3-hydroxypropoxy)benzaldehyde

25 To a solution of 3-hydroxybenzaldehyde (366 mg, 3 mmol) in anhydrous DMF (7 ml), under nitrogen atmosphere, K₂CO₃ (829 mg, 6 mmol), and, after 10 minutes, 3-bromo-1-propanol (500 mg, 3.6 mmol) were added. The mixture was heated to reflux for 2 hours, then water was added and the product was extracted with CH₂Cl₂. The organic layers were washed with water and with NaCl saturated
30 solution, dried on Na₂SO₄. After evaporation of the solvent the crude product was purified by chromatography on silica gel (Petroleum ether/Ethyl acetate 2/1); 520 mg (yield 95%) of title product were obtained.

¹H NMR (300 MHz, CDCl₃): 9.95 (1H, s), 7.43 (2H, m), 7.38 (1H, d, J = 1.8 Hz), 7.17 (1H, m), 4.17 (2H, t, J = 6 Hz), 3.86 (2H, t, J = 6 Hz), 2.06 (2H, tt, J = 6 Hz, 6 Hz).

¹³C NMR (75 MHz, CDCl₃): 192.1, 159.3, 137.7, 130.1, 123.6, 121.8, 112.8, 65.7, 60.0, 31.8.

Step c) Synthesis 5,15-bis-[3-(3-hydroxypropoxy)phenyl]porphyrin

To a solution of 2-(1*H*-pyrrol-2-ylmethyl)-1*H*-pyrrole (236 mg, 1.6 mmol) and 3-(3-hydroxypropoxy)benzaldehyde (305 mg, 1.6 mmol) in dry CH₂Cl₂ (160 ml), trifluoroacetic acid (114 mg, 1 mmol) was added and the mixture was kept under magnetic stirring, at room temperature, under nitrogen atmosphere, for 4 hours. Then *p*-chloranil (492 mg, 2 mmol) was added and the final mixture stirred for additional 5 hours, then the organic phase was washed with Na₂CO₃ saturated solution, dried on Na₂SO₄ and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel (CHCl₃/MeOH 97/3), to give 100 mg of title product (yield 20%).

¹H NMR (300 MHz, CDCl₃): 10.32 (2H, s), 9.39 (4H, d, J = 4.2 Hz), 9.12 (4H, d, J = 4.2 Hz), 7.85 (4H, m), 7.69 (2H, dd, J = 8.4 Hz, 7.5 Hz), 7.36 (2H, dd, J = 8.4 Hz, 2.0 Hz), 4.36 (4H, t, J = 6.0 Hz), 3.96 (4H, t, J = 6.0 Hz), 2.16 (4H, tt, J = 6.0 Hz, 6.0 Hz), -3.15 (2H, s).

¹³C NMR (75 MHz, CDCl₃): 157.3, 146.9, 145.2, 142.7, 131.6, 131.0, 128.0, 127.8, 121.2, 118.7, 114.0, 105.2, 65.9, 60.5, 32.0.

Step d) Synthesis of 5,15-bis-[3-(3-methylsulphonylpropoxy) phenyl]porphyrin

To a solution of 5,15-bis-[3-(3-hydroxypropoxy)phenyl]porphyrin (30 mg, 0.049 mmol) in anhydrous CH₂Cl₂, under nitrogen atmosphere, at 0°C, triethylamine (29 mg, 0.29 mmol) and methansulphonylchloride (17 mg, 0.15 mmol) were added. The mixture was kept under magnetic stirring at 0 °C for 3 hours, then washed with NaHCO₃ saturated solution and with water. The organic phase was dried under Na₂SO₄ and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel (CHCl₃), to obtain 17 mg of the pure title product (yield 45%).

¹H NMR (300 MHz, CDCl₃): 10.33 (2H, s), 9.40 (4H, d, J = 4.8 Hz), 9.12 (4H, d, J = 4.8 Hz), 7.90 (2H, d, J = 7.5 Hz), 7.82 (2H, s), 7.70 (2H, dd, J = 8.4 Hz, 7.5 Hz),

7.35 (2H, d, J = 8.4 Hz), 4.54 (4H, t, J = 6.3 Hz), 4.32 (4H, t, J = 5.7 Hz), 3.02 (6H, s), 2.34 (4H, tt, J = 6.3 Hz, 5.7 Hz), -3.14 (2H, bs).

^{13}C NMR (75 MHz, DMSO- d_6): 157.8, 147.0, 145.5, 142.5, 133.3, 131.5, 128.9, 128.4, 121.7, 119.0, 115.0, 106.4, 98.8, 68.1, 64.6, 37.2, 29.3.

5 ESI-MS: m/z 767.5 Th ($\text{C}_{40}\text{H}_{39}\text{N}_4\text{O}_8\text{S}_2$) $^+$

Step e) Synthesis of 5,15-bis-[3-(3-N,N-dimethylaminopropoxy))phenyl] porphyrin

To a solution of 5,15-bis-[3-(3-methylsulphonylpropoxy)phenyl]porphyrin (15 mg, 0.019 mmol) in anhydrous DMF (2ml), under nitrogen atmosphere, K_2CO_3 (14 mg, 0.11 mmol), and, after 10 minutes, dimethylamine hydrochloride (8 mg, 0.11 mmol) were added. The mixture was heated at 80°C for 15 hours, then water was added and the product was extracted with CH_2Cl_2 . The organic layers were washed with water and with NaCl saturated solution, dried on Na_2SO_4 . After evaporation the crude product was purified by flash chromatography (THF to THF/DMF 9/1). After the chromatography, the product was washed with CHCl_3 /Petroleum Ether 1/1 and 10 mg (yield 80%) of pure title product were obtained.

^1H NMR (300 MHz, $\text{D}_2\text{O}+\text{HCl}$): 10.83 (2H, s), 9.40 (4H, m), 8.95 (4H, m), 7.83 (4H, m), 7.74 (2H, m), 3.38 (4H, m), 3.30 (4H, m), 2.78 (12H, s), 2.19 (4H, m).

^{13}C NMR (75 MHz, $\text{D}_2\text{O}+\text{HCl}$, selected data): 157.7, 145.1, 142.4, 139.8, 131.8, 130.6, 130.3, 129.7, 124.4, 112.1, 116.5, 106.9, 65.7, 55.6, 43.0, 24.3.

ESI-MS: m/z 665.6 Th ($\text{C}_{42}\text{H}_{45}\text{N}_6\text{O}_2$) $^+$

Step f) Synthesis of 5,15-bis-[3-(3-N,N,N-trimethylammonium)propoxyphenyl]porphyrin diiodide

To a solution of 5,15-bis-[3-(3-N,N-dimethylaminopropoxy)phenyl] porphyrin (26 mg, 0.039 mmol) in dry NMP (5 ml), iodomethane (110 mg, 0.78 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 24 hours, then diethyl ether was added slowly until a precipitate appeared. The suspension was filtered and the solid crystallized from MeOH/diethyl ether to give 26 mg of pure title product (yield 70%).

^1H NMR (300 MHz, DMSO- d_6): 10.64 (2H, s), 9.66 (4H, d, J = 4.6 Hz), 9.07 (4H, d, J = 4.6 Hz), 7.86 (4H, m), 7.80 (2H, dd, J = 8.1 Hz, 7.0 Hz), 7.48 (2H, d, J = 7.0

Hz), 4.32 (4H, t, J = 5.7 Hz), 3.58 (4H, m), 3.10 (18H, s), 2.29 (4H, m), -3.29 (2H, s).

^{13}C NMR (75 MHz, DMSO- d_6 , selected data): 157.5, 146.8, 145.3, 142.3, 133.0, 131.2, 128.8, 121.6, 118.7, 114.8, 108.6, 106.2, 65.6, 63.6, 52.8, 23.1.

5 UV-VIS (DMF): λ_{max} 670, 629, 575, 535, 500, 381, 256, 244.

ESI-MS: m/z 347.4 Th ($\text{C}_{44}\text{H}_{50}\text{N}_6\text{O}_2$) $^{2+}$

According to the procedures described in Example 25 the following porphyrins have been prepared:

EXAMPLE 26

10 5,15-bis-[4-(2-piperidin-1-ylethoxy)phenyl]porphyrin

ESI-MS: m/z 717.4 Th ($\text{C}_{46}\text{H}_{49}\text{N}_6\text{O}_2$) $^+$

EXAMPLE 27

5,15-bis-[4-(2-N-methylpiperidin-1-iumethoxy)phenyl]porphyrin diiodide

ESI-MS: m/z 373.2 Th ($\text{C}_{48}\text{H}_{54}\text{N}_6\text{O}_2$) $^{2+}$

15 **EXAMPLE 28**

5,15-bis-[4-(3-N,N-dimethylaminopropoxy)phenyl]-10,20-bis-[(3-decyloxy)phenyl]porphyrin

ESI-MS: m/z 1129.7 Th ($\text{C}_{74}\text{H}_{93}\text{N}_6\text{O}_4$) $^+$

EXAMPLE 29

20 5,15-bis-[4-[3-N,N,N-trimethylammoniumpropoxy)phenyl]-10,20-bis-[(3-decyloxy)phenyl]porphyrin diiodide

ESI-MS: m/z 579.3 Th ($\text{C}_{76}\text{H}_{98}\text{N}_6\text{O}_4$) $^{2+}$

EXAMPLE 30

5,15-bis 4-{[2-(N,N-dimethylamino)ethylthio]phenyl} porphyrin

25 ESI-MS: m/z 669.39Th ($\text{C}_{40}\text{H}_{41}\text{N}_6\text{S}_2$) $^+$

EXAMPLE 31

5,15-bis-{4-[2-(N,N,N-trimethylammonium)ethylthio]phenyl}porphyrin diiodide

ESI-MS: m/z 349.4 Th ($\text{C}_{42}\text{H}_{46}\text{N}_6\text{S}_2$) $^{2+}$

EXAMPLE 32

30 5,15-bis-{4-[2-[3-(trimethylammonium)phenoxy]ethoxy]phenyl} porphyrin diiodide

ESI-MS: m/z 425.2 Th ($\text{C}_{54}\text{H}_{54}\text{N}_6\text{O}_4$) $^{2+}$

EXAMPLE 33

5,15-bis-[4-[2-[3-(N,N,N-trimethylammonium)phenyl]-2-oxoethyl]-10,20-bis-[(3-decyloxy)phenyl]porphyrin diiodide

ESI-MS: m/z 639.4 Th ($C_{86}H_{98}N_6O_4$)²⁺

EXAMPLE 34

5 Synthesis of 5,15-bis-[3-(3-N,N,N-trimethylammoniumpropoxy)phenyl]porphyrinate zinc(II) diiodide

Step a) Synthesis of 5,15-bis-[3-(3-hydroxypropoxy)phenyl]porphyrinate zinc(II)

To a solution of 5,15-bis-[3-(3-hydroxypropoxy)phenyl]porphyrin (100 mg, 0.16 mmol) in $CHCl_3/THF$ 1/1 (10 ml), zinc acetate (183 mg, 1 mmol) was added and
10 the mixture was kept under magnetic stirring, at 40°C, under nitrogen for 4 hours. Then the solid was filtered through celite and the liquid phase was dried on Na_2SO_4 , then the solvent removed by evaporation to obtain 110 mg of title product (yield 98%) that was used in the following step without further purification.

¹H NMR (300 MHz, $CDCl_3$): 10.24 (2H, s), 9.35 (4H, d, J = 4.5 Hz), 9.08 (4H, d, J =
15 4.5 Hz), 7.81 (2H, d, J = 8.1 Hz), 7.63 (2H, s), 7.58 (2H, dd, J = 8.1 Hz, 7.5 Hz), 7.12 (2H, d, J = 7.5 Hz), 3.96 (4H, m), 3.25 (4H, m), 1.66 (4H, m).

¹³C NMR (75 MHz, $CDCl_3$): 156.9, 149.9, 149.7, 144.0, 132.4, 131.7, 127.9, 127.3, 121.0, 119.5, 113.7, 106.1, 65.9, 60.3, 31.7.

20 Step b) Synthesis of 5,15-bis-[3-(3-methylsulphonylpropoxy)phenyl]porphyrinate zinc(II)

To a solution of 5,15-bis-[3-(3-hydroxypropoxy)phenyl]porphyrinate zinc (100 mg, 0.14 mmol) in anhydrous CH_2Cl_2 , under nitrogen atmosphere, at 0°C, triethylamine (43 mg, 0.42 mmol) and methansulphonylchloride (36 mg, 0.31 mmol) were added. The mixture was kept under magnetic stirring at 0°C for 2 hours, then
25 washed with $NaHCO_3$ saturated solution and with water. The organic phase was dried on Na_2SO_4 and the solvent removed by evaporation. The crude product was purified by flash chromatography on silica gel ($CHCl_3/MeOH$ 99/1), to obtain 70 mg of the pure title product (yield 60%).

¹H NMR (300 MHz, $CDCl_3$): 10.33 (2H, s), 9.44 (4H, d, J = 4.5 Hz), 9.17 (4H, d, J =
30 4.5 Hz), 7.89 (2H, d, J = 7.8 Hz), 7.82 (2H, s), 7.69 (2H, dd, J = 8.1 Hz, 7.8 Hz), 7.35 (2H, d, J = 8.1 Hz), 4.53 (4H, t, J = 6.0 Hz), 4.31 (4H, t, J = 6 Hz), 3.02 (6H, s), 2.33 (4H, tt, J = 6.0 Hz, 6.0 Hz).

^{13}C NMR (75 MHz, CDCl_3): 156.9, 149.9, 149.5, 144.0, 132.5, 131.8, 128.0, 127.6, 121.0, 119.6, 113.8, 106.3, 66.8, 63.4, 37.2, 29.2.

APCI-MS: m/z 829.1 Th ($\text{C}_{40}\text{H}_{39}\text{N}_4\text{O}_8\text{S}_2\text{Zn}$) $^+$

Step c) Synthesis of 5,15-bis-[3-(3-N,N-dimethylaminopropoxy))phenyl]

5 porphyrinate zinc(II)

To a solution of 5,15-bis-[3-(3-methylsulphonylpropoxy)phenyl] porphyrinate zinc (15 mg, 0.019 mmol) in anhydrous DMF (2 ml), under nitrogen atmosphere, K_2CO_3 (14 mg, 0.11 mmol), and, after 10 minutes, dimethylamine hydrochloride (8 mg, 0.11 mmol) were added. The mixture was heated at 80°C for 15 hours, then water was added and the product was extracted with CH_2Cl_2 . The organic layers were washed with water and with NaCl saturated solution, then dried on Na_2SO_4 . After evaporation the crude product was purified by chromatography (THF to THF/DMF 9/1). After the chromatography, the product was washed with CHCl_3 /Petroleum Ether 1/1 and 10 mg (yield 80%) of pure product of the title were obtained.

15 ^1H NMR (300 MHz, $\text{D}_2\text{O}+\text{HCl}$): 11.16 (2H, s), 9.67 (4H, d, $J = 4.5$ Hz), 9.17 (4H, m), 8.05 (2H, d, $J = 9.0$ Hz), 7.82 (2H, dd, $J = 9.0$ Hz, 8.4 Hz), 7.51 (2H, d, $J = 8.4$ Hz), 4.32 (4H, m), 3.35 (4H, t, $J = 8.2$ Hz), 2.82 (12H, s), 2.23 (4H, m).

^{13}C NMR (75 MHz, $\text{D}_2\text{O}+\text{HCl}$, selected data): 157.8, 145.5, 142.8, 140.1, 131.9, 131.0, 129.6, 124.8, 121.5, 116.5, 107.1, 65.8, 55.7, 43.0, 24.3.

20 UV-VIS (DMF): λ_{max} 544, 406, 310, 255, 244.

APCI-MS: m/z 727.0 Th ($\text{C}_{42}\text{H}_{45}\text{N}_6\text{O}_2\text{Zn}$) $^+$

Step d) Synthesis of 5,15-bis-[3-(3-N,N,N-trimethylammoniumpropoxy)phenyl]porphyrinate zinc(II) diiodide

To a solution of 5,15-bis-[3-(3-N,N-dimethylaminopropoxy)phenyl] porphyrinate zinc (64 mg, 0.088 mmol) in dry NMP (5 ml), iodomethane (374 mg, 2.63 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 24 hours, then diethyl ether was added slowly until a precipitate appeared. The suspension was filtered and the solid crystallized from MeOH/diethyl ether to give 70 mg of pure title product (yield 80%).

30 ^1H NMR (300 MHz, $\text{DMSO}-d^6$): 10.35 (2H, s), 9.48 (4H, d, $J = 4.2$ Hz), 8.98 (4H, d, $J = 4.2$ Hz), 7.79 (4H, m), 7.73 (2H, dd, $J = 9.3$ Hz, 7.0 Hz), 7.42 (2H, d, $J = 9.3$ Hz), 4.31 (4H, t, $J = 6.0$ Hz), 3.57 (4H, m), 3.10 (18H, s), 2.48 (4H, m).

^{13}C NMR (75 MHz, DMSO- d_6 , selected data): 157.3, 149.7, 149.6, 132.8, 132.3, 128.3, 121.7, 119.2, 114.3, 106.8, 65.7, 63.7, 52.9, 23.4.

UV-VIS (DMF): λ_{max} 544, 408, 392, 312, 264.

ESI-MS: m/z 347.4 Th ($\text{C}_{44}\text{H}_{50}\text{N}_6\text{O}_2\text{Zn}$) $^{2+}$

5 EXAMPLE 35

Synthesis of 5,15-bis-[4-(4-N,N,N-trimethylammoniumphenoxy)phenyl] porphyrin diiodide

Step a) Synthesis of 4-(4-nitrophenoxy)benzaldehyde

To a solution of 4-hydroxybenzaldehyde (366 mg, 3 mmol) in anhydrous DMF (7 ml), under nitrogen atmosphere, K_2CO_3 (829 mg, 6 mmol), and, after 10 minutes, 4-bromonitrobenzene (726 mg, 3.6 mmol) were added. The mixture was heated to reflux for 3 hours, then water was added and the product was extracted with CH_2Cl_2 . The organic layers were washed with water and with NaCl saturated solution and dried with Na_2SO_4 . After evaporation of the solvent the crude product was purified by chromatography on silica gel (Petroleum ether/Ethyl acetate 5/1); 605 mg (yield 82%) of pure title product were obtained.

^1H NMR (300 MHz, CDCl_3): 9.99 (1H, s), 8.27 (2H, m), 7.94 (2H, m), 7.20 (2H, m), 7.14 (2H, m).

^{13}C NMR (75 MHz, CDCl_3): 190.7, 161.5, 160.6, 133.2, 132.3, 126.3, 119.9, 119.0.

20 Step c) Synthesis of 5,15-bis-[4-(4-nitrophenoxy)phenyl]porphyrin

To a solution of 2-(1*H*-pyrrol-2-ylmethyl)-1*H*-pyrrole (200 mg, 1.37 mmol) and 4-(4-nitrophenoxy)benzaldehyde (305 mg, 1.6 mmol) in dry CH_2Cl_2 (130 ml), trifluoroacetic acid (114 mg, 1 mmol) was added and the mixture was kept under magnetic stirring, at room temperature, under nitrogen atmosphere for 3 hours, then *p*-chloranil (492 mg, 2 mmol) was added and the final mixture stirred for additional 15 hours, then the organic phase was washed with Na_2CO_3 saturated solution, dried with Na_2SO_4 and the solvent removed by evaporation. The crude product was purified by chromatography on silica gel (CHCl_3 /Petroleum ether 3/1), to give 45 mg of title product (yield 10%).

30 ^1H NMR (300 MHz, CDCl_3): 10.37 (2H, s), 9.45 (4H, d, $J = 4.5$ Hz), 9.12 (4H, d, $J = 4.5$ Hz), 8.41 (4H, m), 8.34 (4H, m), 7.54 (4H, m), 7.41 (4H, m), -3.11 (2H, bs).

^{13}C NMR (75 MHz, CDCl_3 , selected data): 154.9, 147.1, 145.3, 140.1, 138.4, 136.4, 132.0, 130.8, 128.6, 126.3, 126.2, 118.9, 117.7, 105.6.

UV-VIS (DMF): λ_{max} 629, 574, 535, 409, 395, 382, 305, 249, 233.

ESI-MS: m/z 737.3 Th ($\text{C}_{44}\text{H}_{29}\text{N}_8\text{O}_6$) $^+$

5 Step d) Synthesis of 5,15-bis-[4-(4-aminophenoxy)phenyl]porphyrin

To a solution of 5,15-bis-[4-(4-nitrophenoxy)phenyl]porphyrin (70 mg, 0.095 mmol) in CHCl_3 (10 ml), saturated with concentrated HCl, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (105 mg, 0.475 mmol) was added and the mixture was kept under magnetic stirring, at room temperature for 24 h, then cold water was added, the mixture was neutralized with
10 a solution 15% of ammonia, and the organic phase was extracted, dried on Na_2SO_4 , then the solvent was removed by evaporation. The crude product was purified by chromatography on silica gel (THF to THF/DMF 9/1), to give 43 mg of title product (yield 67%).

^1H NMR (300 MHz, CDCl_3): 10.31 (2H, s), 9.40 (4H, d, $J = 4.8$ Hz), 9.12 (4H, d, $J =$
15 4.8 Hz), 8.16 (4H, m), 7.35 (4H, m), 7.21 (4H, m), 6.86 (4H, m), -3.10 (2H, s).

^{13}C NMR (75 MHz, CDCl_3 , selected data): 159.1, 148.5, 147.4, 145.1, 136.5, 135.9, 131.6, 131.0, 126.2, 121.7, 118.9, 117.7, 116.4, 115.5, 105.2.

UV-VIS (DMF): λ_{max} 630, 576, 536, 501, 382, 265, 253.

ESI-MS: m/z 677.3 Th ($\text{C}_{44}\text{H}_{33}\text{N}_6\text{O}_2$) $^+$

20 Step f) Synthesis of 5,15-bis-[4-(4-N,N,N-trimethylammoniumphenoxy)phenyl]porphyrin diiodide

To a solution of 5,15-bis-[4-(4-aminophenoxy)phenyl]porphyrin (30 mg, 0.042 mmol) in dry NMP (5 ml), iodomethane (150 mg, 1.1 mmol) was added. The reaction mixture was kept under magnetic stirring, at room temperature, for 24
25 hours, then diethyl ether was added slowly until a precipitate appeared. The suspension was filtered and the solid crystallized from MeOH/diethyl ether to give 35 mg of pure title product (yield 80%).

^1H NMR (300 MHz, DMSO-d_6): 10.66 (2H, s), 9.71 (4H, d, $J = 4.8$ Hz), 9.12 (4H, d, $J =$
30 4.8 Hz), 8.35 (4H, m), 8.14 (4H, m), 7.58 (8H, m), 3.68 (18H, m), -3.27 (2H, s).

^{13}C NMR (75 MHz, DMSO-d_6 , selected data): 156.3, 147.1, 142.9, 136.8, 133.2, 131.4, 123.3, 120.0, 118.5, 115.3, 111.2, 106.4, 98.6, 57.2.

UV-VIS (DMF): λ_{max} 577, 539, 502, 392, 265, 254, 244, 235.

ESI-MS: m/z 381.3 Th ($C_{50}H_{46}N_6O_2$)²⁺

According to the procedures described in Example 35 the following porphyrins have been prepared:

EXAMPLE 36

5 5,15-bis-[3-(4-N,N-dimethylaminophenoxy)phenyl]porphyrin

ESI-MS: m/z 733.3 Th ($C_{48}H_{41}N_6O_2$)⁺

EXAMPLE 37

5,15-bis-[3-(4-N,N,N-trimethylammoniumphenoxy)phenyl]porphyrin diiodide

ESI-MS: m/z 381.2 Th ($C_{50}H_{46}N_6O_2$)²⁺

10 EXAMPLE 38

5,15-bis-[3-(4-N,N-dimethylaminophenyl)thiophenyl]porphyrin

ESI-MS: m/z 765.3 Th ($C_{48}H_{41}N_6S_2$)⁺

EXAMPLE 39

5,15-bis-[3-(4-N,N,N-trimethylammoniumthiophenoxy)phenyl]porphyrin diiodide

15 ESI-MS: m/z 795.3 Th ($C_{48}H_{41}N_6O_2$)²⁺

EXAMPLE 40

5,15-bis-4-[3-(N,N-dimethylaminophenoxy)phenyl]-10,20-bis-[(4-decyloxy)phenyl]porphyrin

ESI-MS: m/z 1197.6 Th ($C_{80}H_{89}N_6O_4$)²⁺

20 EXAMPLE 41

5,15-bis-4-[3-(N,N,N-trimethylammoniumphenoxy)phenyl]-10,20-bis-[(4-decyloxy)phenyl]porphyrin diiodide

ESI-MS: m/z 795.3 Th ($C_{82}H_{94}N_6O_4$)²⁺

According with the procedure reported in Examples 1 and 34 or by metallation of metal free porphyrins, the following Zn(II)-porphyrinates have been prepared:

25 EXAMPLE 42

5,10,15-tris-{4-[4-(N,N-dimethylamino)butoxy]phenyl}-20-[(4-undecyloxy)phenyl]porphyrinate zinc(II)

ESI-MS: m/z 1194.9 Th [$C_{73}H_{90}N_7O_4Zn$]⁺

30 EXAMPLE 43

5,10,15-tris-{4-[4-(N,N,N-trimethylammonium)butoxy]phenyl}-20-[(4-

undecyloxy)phenyl]porphyrinate zinc(II) triiodide

ESI-MS: m/z 418.3 Th $[\text{C}_{77}\text{H}_{102}\text{N}_7\text{O}_4\text{Zn}]^{3+}$

EXAMPLE 44

5,15-bis-[4-(2-piperidin-1-ylethoxy)phenyl]porphyrinate zinc(II)

5 ESI-MS: m/z 780.3 Th $(\text{C}_{46}\text{H}_{47}\text{N}_6\text{O}_2\text{Zn})^+$

EXAMPLE 45

5,15-bis-[4-(2-N-methylpiperidin-1-iumethoxy)phenyl]porphyrinate zinc(II) diiodide

ESI-MS: m/z 405.2 Th $(\text{C}_{48}\text{H}_{52}\text{N}_6\text{O}_2\text{Zn})^{2+}$